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Signed R. Mahoney

Dated 6 January 2004

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P01/7700 0.00-0227702.8

Patents Form 1/77

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Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

The Patent Office

Cardiff Road
Newport
Gwent NP9 1RH

1. Your reference — 100861

2. Patent application number *(The Patent Office will fill in this part)* — 0227702.8 — 28 NOV 2002

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

AstraZeneca AB
S-151 85 Sodertalje
Sweden

78224482003

Patents ADP number *(if you know it)*

If the applicant is a corporate body, give the country/state of its incorporation — Sweden

4. Title of the invention

CHEMICAL COMPOUNDS

5. Name of your agent *(if you have one)*

Dr Anne Williams

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

AstraZeneca UK Limited
Global Intellectual Property
Mereside, Alderley Park
Macclesfield
Cheshire SK10 4TG

Patents ADP number *(if you know it)*

78224710002

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*

a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is not named as an applicant, or
c) any named applicant is a corporate body.
See note (d))

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	
Description	68 ✓
Claim(s)	13 ✓
Abstract	
Drawing(s)	

10. If you are also filing any of the following, state how many against each item.

Priority documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. I/We request the grant of a patent on the basis of this application.

Signature Authorised Signatory Date 27/11/2002

12. Name and daytime telephone number of person to contact in the United Kingdom: Jennifer C Bennett - 01625 230148

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Notes

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CHEMICAL COMPOUNDS

The present invention relates to antibiotic compounds and in particular to antibiotic compounds containing substituted oxazolidinone and/or isoxazoline rings. This invention further relates to processes for their preparation, to intermediates useful in their preparation, to their use as therapeutic agents and to pharmaceutical compositions containing them.

The international microbiological community continues to express serious concern that the evolution of antibiotic resistance could result in strains against which currently available antibacterial agents will be ineffective. In general, bacterial pathogens may be classified as either Gram-positive or Gram-negative pathogens. Antibiotic compounds with effective activity against both Gram-positive and Gram-negative pathogens are generally regarded as having a broad spectrum of activity. The compounds of the present invention are regarded as effective against both Gram-positive and certain Gram-negative pathogens.

Gram-positive pathogens, for example Staphylococci, Enterococci, Streptococci and mycobacteria, are particularly important because of the development of resistant strains which are both difficult to treat and difficult to eradicate from the hospital environment once established. Examples of such strains are methicillin resistant staphylococcus (MRSA), methicillin resistant coagulase negative staphylococci (MRCNS), penicillin resistant Streptococcus pneumoniae and multiply resistant Enterococcus faecium.

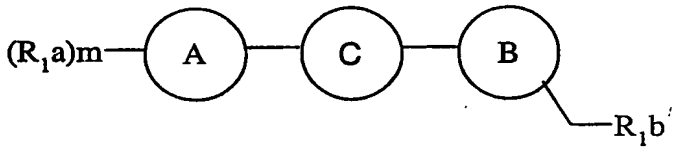
The major clinically effective antibiotic for treatment of such resistant Gram-positive pathogens is vancomycin. Vancomycin is a glycopeptide and is associated with various toxicities including nephrotoxicity. Furthermore, and most importantly, antibacterial resistance to vancomycin and other glycopeptides is also appearing. This resistance is increasing at a steady rate rendering these agents less and less effective in the treatment of Gram-positive pathogens. There is also now increasing resistance appearing towards agents such as β-lactams, quinolones and macrolides used for the treatment of upper respiratory tract infections, also caused by certain Gram negative strains including H.influenzae and M.catarrhalis.

Certain antibacterial compounds containing an oxazolidinone ring have been described in the art (for example, Walter A. Gregory et al in J.Med.Chem. 1990, 33, 2569-2578 and 1989, 32(8), 1673-81; Chung-Ho Park et al in J.Med.Chem. 1992, 35, 1156-1165). Bacterial resistance to known antibacterial agents may develop, for example, by (i) the evolution of active binding sites in the bacteria rendering a previously active pharmacophore less effective

or redundant, and/or (ii) the evolution of means to chemically deactivate a given pharmacophore, and/or (iii) the evolution of efflux pathways. Therefore, there remains an ongoing need to find new antibacterial agents with a favourable pharmacological profile, in particular for compounds containing new, more potent, pharmacophores.

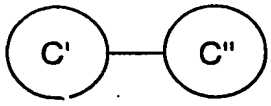
We have discovered a class of bi-aryl antibiotic compounds containing two substituted oxazolidinone and/or isoxazoline rings which has useful activity against Gram-positive pathogens including MRSA and MRCNS and, in particular, against various strains exhibiting resistance to vancomycin and/or linezolid and against E. faecium strains resistant to both aminoglycosides and clinically used β-lactams, but also to fastidious Gram negative strains such as H.influenzae, M.catarrhalis, mycoplasma spp. and chlamydial strains. The compounds of the invention contain two groups capable of acting as pharmacophores. The two groups may independently bind at pharmacophore binding sites where the sites may be similar or different, where the similar or different sites may be occupied simultaneously or not simultaneously within a single organism, or where the relative importance of different binding modes to the similar or different sites may vary between two organisms of different genus. Alternatively one of the groups may bind at a pharmacophore binding site whilst the other group fulfills a different role in the mechanism of action.

Accordingly the present invention provides a compound of the formula (I), or a pharmaceutically-acceptable salt, or an in-vivo-hydrolysable ester thereof,

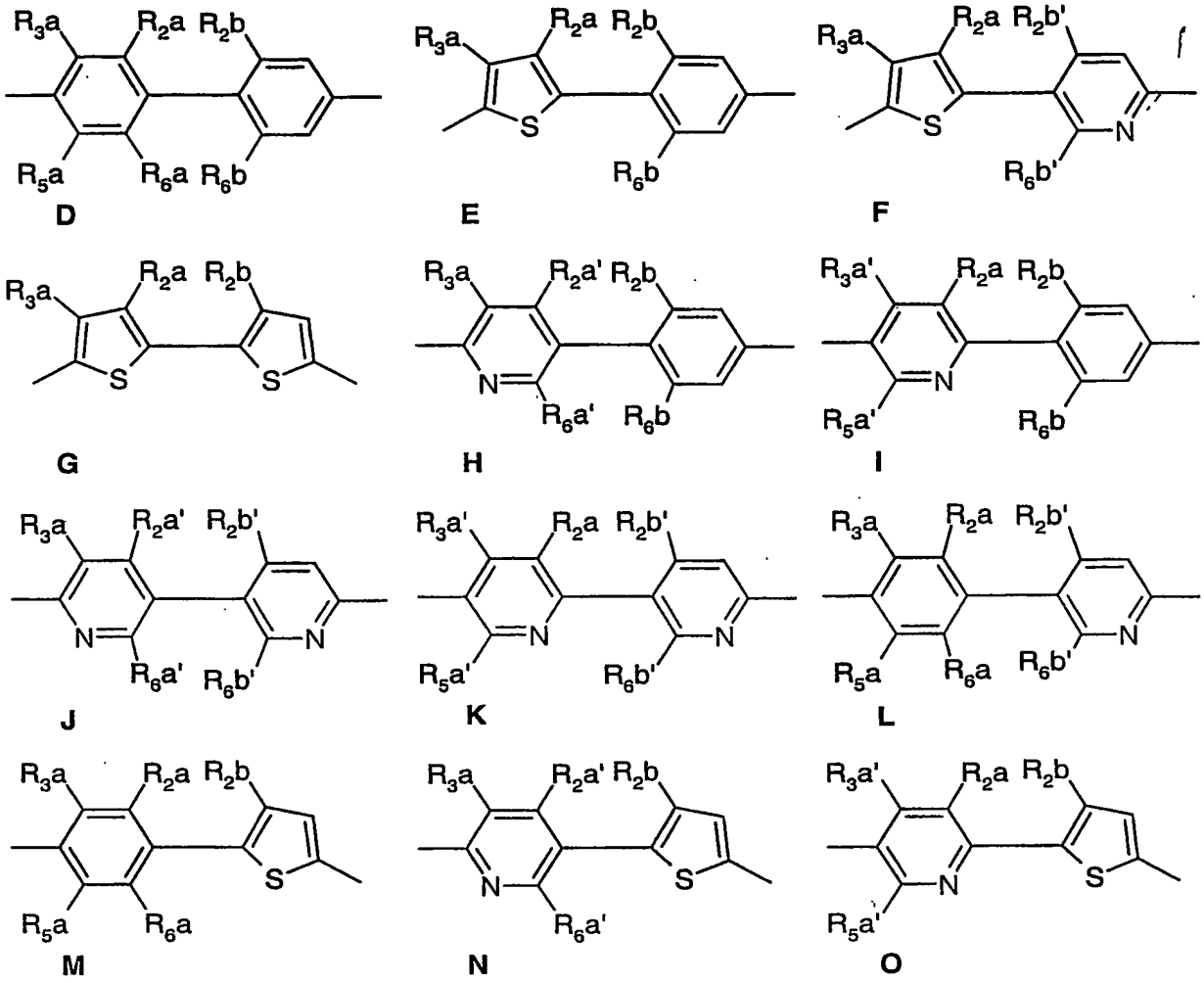


(I)

wherein in (I) C is a biaryl group C'-C''



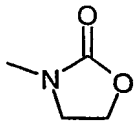
where C' and C'' are independently aryl or heteroaryl rings such that the group C is represented by any one of the groups D to O below:



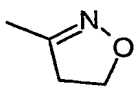
wherein the groups D to O are attached to rings A and B in the orientation [(A-C') and (C''-B)] shown;

wherein A and B are independently selected from

i) ii)



and



wherein A is linked as shown in (I) via the 3-position to ring C' of group C and independently substituted in the 4 and 5 positions as shown in (I) by one or more substituents $-(R_1a)m$; and wherein B is linked as shown in (I) via the 3-position to ring C'' of group C and independently substituted in the 5 position as shown in (I) by substituent $-CH_2-R_1b$;

R_2b and R_6b are independently selected from H, F, Cl, OMe, Me, Et and CF_3;

R_2b' and R_6b' are independently selected from H, OMe, Me, Et and CF_3;

R_2a and R_6a are independently selected from H, Br; F, Cl, OMe, SMe; Me, Et and CF_3;

R_2a' and R_6a' are independently selected from H, OMe, SMe; Me, Et and CF_3;

R_3a and R_5a are independently selected from H, (1-4C)alkyl, Br, F, Cl, OH, (1-4C)alkoxy, $-S(O)_n$(1-4C)alkyl (wherein n = 0,1,or 2), amino, (1-4C)alkylcarbonylamino-, nitro, cyano, -CHO, -CO(1-4C) alkyl, $-CONH_2$ and -CONH(1-4C)alkyl;

R_3a', R_5a' are independently selected from H, (1-4C)alkyl, OH, (1-4C)alkoxy, (1-4C)alkylthio, amino, (1-4C)alkylcarbonylamino-, nitro, cyano, -CHO, -CO(1-4C)alkyl, $-CONH_2$ and -CONH(1-4C)alkyl;

wherein one of R_3a, R_5a, R_3a', R_5a'taken together with a substituent R_1a at position 4 of ring A and rings A and C' may form a 5-7 membered ring;

wherein any (1-4C)alkyl group may be optionally substituted with F, OH, (1-4C)alkoxy, $-S(O)_n$(1-4C)alkyl (wherein n = 0,1,or 2) or cyano;

wherein when ring C' is a pyridine ring (ie when group C is group H, I, J, K, N or O) the ring nitrogen may optionally be oxidised to an N-oxide;

R_1a is independently selected from R_1a1 to R_1a4 below:

R_1a1: AR1, AR2, AR2a, AR2b, AR3, AR3a, AR3b, AR4, AR4a, CY1, CY2;

R_1a2: cyano, carboxy, (1-4C)alkoxycarbonyl, -C(=W)NRvRw [wherein W is O or S, Rv and Rw are independently H, or (1-4C)alkyl and wherein Rv and Rw taken together with the amide or thioamide nitrogen to which they are attached can form a 5-7 membered ring optionally with an additional heteroatom selected from N, O, S(O)n in place of 1 carbon atom of the so formed ring; wherein when said ring is a piperazine ring, the ring may be optionally substituted on the additional nitrogen by a group selected from (1-4C)alkyl, (1-4C)cycloalkyl, (1-4C)acyl, -COO(1-4C)alkyl, S(O)n(1-4C)alkyl (wherein n = 1 or 2), -COOAR1, -CS(1-4C)alkyl) and –C(=S)O(1-4C)alkyl; wherein any (1-4C)alkyl, (1-4C)acyl and (1-4C)cycloalkyl substituent may itself be substituted by cyano, hydroxy or halo; provided that, such a substituent is not on a carbon adjacent to a nitrogen atom of the piperazine ring], ethenyl, 2-(1-4C)alkylethenyl, 2-cyanoethenyl, 2-cyano-2-((1-4C)alkyl)ethenyl, 2-nitroethenyl, 2-nitro-2-((1-4C)alkyl)ethenyl, 2-((1-4C)alkylaminocarbonyl)ethenyl, 2-((1-4C)alkoxycarbonyl)ethenyl, 2-(AR1)ethenyl, 2-(AR2)ethenyl, 2-(AR2a)ethenyl;

R_1a3: (1-10C)alkyl

{optionally substituted by one or more groups (including geminal disubstitution) each independently selected from hydroxy, (1-10C)alkoxy, (1-4C)alkoxy-(1-4C)alkoxy,

(1-4C)alkoxy-(1-4C)alkoxy-(1-4C)alkoxy, (1-4C)alkylcarbonyl, phosphoryl [-O-P(O)(OH)$_2$, and mono- and di-(1-4C)alkoxy derivatives thereof], phosphiryl [-O-P(OH)$_2$ and mono- and di-(1-4C)alkoxy derivatives thereof], and amino; and/or optionally substituted by one group selected from carboxy, phosphonate [phosphono, -P(O)(OH)$_2$, and mono- and di-(1-4C)alkoxy derivatives thereof], phosphinate [-P(OH)$_2$ and mono- and di-(1-4C)alkoxy derivatives thereof], cyano, halo, trifluoromethyl, (1-4C)alkoxycarbonyl, (1-4C)alkoxy-(1-4C)alkoxycarbonyl, (1-4C)alkoxy-(1-4C)alkoxy-(1-4C)alkoxycarbonyl, (1-4C)alkylamino, di((1-4C)alkyl)amino, (1-6C)alkanoylamino-, (1-4C)alkoxycarbonylamino-, N-(1-4C)alkyl-N-(1-6C)alkanoylamino-, -C(=W)NRvRw [wherein W is O or S, Rv and Rw are independently H, or (1-4C)alkyl and wherein Rv and Rw taken together with the amide or thioamide nitrogen to which they are attached can form a 5-7 membered ring optionally with an additional heteroatom selected from N, O, S(O)n in place of 1 carbon atom of the so formed ring; wherein when said ring is a piperazine ring, the ring may be optionally substituted on the additional nitrogen by a group selected from (1-4C)alkyl, (1-4C)cycloalkyl, (1-4C)acyl, -COO(1-4C)alkyl, S(O)n(1-4C)alkyl (wherein n = 1 or 2), -COOAR1, -CS(1-4C)alkyl and –C(=S)O(1-4C)alkyl], (=NORv) wherein Rv is as hereinbefore defined, (1-4C)alkylS(O)$_p$NH-, (1-4C)alkylS(O)$_p$-((1-4C)alkyl)N-, fluoro(1-4C)alkylS(O)$_p$NH-, fluoro(1-4C)alkylS(O)$_p$((1-4C)alkyl)N-, (1-4C)alkylS(O)$_q$-, CY1, CY2, AR1, AR2, AR3, AR1-O-, AR2-O-, AR3-O-, AR1-S(O)$_q$- , AR2-S(O)$_q$- , AR3-S(O)$_q$- , AR1-NH-, AR2-NH-, AR3-NH- (p is 1 or 2 and q is 0, 1 or 2), and also AR2a, AR2b, AR3a and AR3b versions of AR2 and AR3 containing groups}; wherein any (1-4C)alkyl, (1-4C)acyl and (1-4C)cycloalkyl present in any substituent on R$_1$a3 may itself be substituted by one or two groups selected from cyano, hydroxy, halo, amino, (1-4C)alkylamino and di(1-4C)alkylamino , provided that such a substituent is not on a carbon adjacent to a heteroatom atom if present;

R$_1$a4: R^{14}C(O)O(1-6C)alkyl wherein R^{14} is AR1, AR2, AR2a, AR2b, (1-4C)alkylamino, benzyloxy-(1-4C)alkyl or (1-10C)alkyl {optionally substituted as defined for (R$_1$a3);

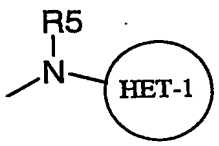
m is 0, 1 or 2;

wherein two substituents R$_1$a both at the 4 or 5 position of ring A taken together may form a 5 to 7 membered spiro ring;

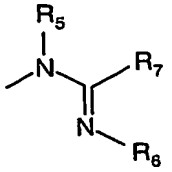
wherein two substituents R$_1$a at the 4 and 5 positions of ring A taken together may form a 5 to 7 membered fused ring;

provided that if (R$_1$a)m is a single substituent R$_1$a at the 5 position of ring A then R$_1$a is not -CH$_2$X wherein X is selected from R1b;

R_1b is independently selected from hydroxy, -OSi(tri-(1-6C)alkyl) (wherein the 3 (1-6C)alkyl groups are independently selected from all possible (1-6C)alkyl groups), $-NR_5C(=W)R_4$, $-OC(=O)R_4$,

a) 

, b) 

and c) 

wherein W is O or S;

provided that if group C is group H or group I, and if one of substituents R_2b and R_6b is H and the other is F, and if all of substituents R_2a, R_6a, R_2a', R_6a', R_3a, R_5a, R_3a', R_5a' are H at each occurrence,then R_1b is not –NHC(=O)Me;

R_4 is hydrogen, amino, (1-8C)alkyl, $-NHR_{12}$, $-N(R_{12})(R_{13})$, $-OR_{12}$ or $-SR_{12}$, (2-4C)alkenyl, -(1-8C)alkylaryl, mono-, di-, tri- and per-halo(1-8C)alkyl, $-(CH_2)p$(3-6C)cycloalkyl or $-(CH_2)p$(3-6C)cycloalkenyl wherein p is 0, 1 or 2;

R_5 is hydrogen, (3-6C)cycloalkyl, phenyloxycarbonyl, tert-butoxycarbonyl, fluorenyloxycarbonyl, benzyloxycarbonyl, (1-6C)alkyl (optionally substituted by cyano or (1-4C)alkoxycarbonyl), $-CO_2R_8$, $-C(=O)R_8$, $-C(=O)SR_8$, $-C(=S)R_8$, $P(O)(OR_9)(OR_{10})$ and $–SO_2R_{11}$, wherein R_8, R_9, R_{10} and R_{11} are as defined hereinbelow;

HET-1 is selected from HET-1A and HET-1B wherein:

HET-1A is a C-linked 5-membered heteroaryl ring containing 2 to 4 heteroatoms independently selected from N, O and S; which ring is optionally substituted on a C atom by an oxo or thioxo group; and/or which ring is optionally substituted on any available C atom by one or two substituents selected from RT as hereinafter defined and/or on an available nitrogen atom, (provided that the ring is not thereby quaternised) by (1-4C)alkyl;

HET-1B is a C-linked 6-membered heteroaryl ring containing 2 or 3 nitrogen heteroatoms, which ring is optionally substituted on a C atom by an oxo or thioxo group; and/or which ring is optionally substituted on any available C atom by one, two or three substituents selected from RT as hereinafter defined and/or on an available nitrogen atom, (provided that the ring is not thereby quaternised) by (1-4C)alkyl;

HET-2 is selected from HET-2A and HET-2B wherein

HET-2A is an N-linked 5-membered, fully or partially unsaturated heterocyclic ring,

containing either (i) 1 to 3 further nitrogen heteroatoms or (ii) a further heteroatom selected from O and S together with an optional further nitrogen heteroatom; which ring is optionally substituted on a C atom, other than a C atom adjacent to the linking N atom, by an oxo or thioxo group; and/or which ring is optionally substituted on any available C atom, other than a C atom adjacent to the linking N atom, by a substituent selected from RT as hereinafter defined and/or on an available nitrogen atom, other than a N atom adjacent to the linking N atom, (provided that the ring is not thereby quaternised) by (1-4C)alkyl;

HET-2B is an N-linked 6-membered di-hydro-heteroaryl ring containing up to three nitrogen heteroatoms in total (including the linking heteroatom), which ring is substituted on a suitable C atom, other than a C atom adjacent to the linking N atom, by oxo or thioxo and/or which ring is optionally substituted on any available C atom, other than a C atom adjacent to the linking N atom, by one or two substituents independently selected from RT as hereinafter defined and/or on an available nitrogen atom, other than a N atom adjacent to the linking N atom, (provided that the ring is not thereby quaternised) by (1-4C)alkyl;

RT is selected from a substituent from the group:

(RTa1) hydrogen, halogen, (1-4C)alkoxy, (2-4C)alkenyloxy, (2-4C)alkenyl, (2-4C)alkynyl, (3-6C)cycloalkyl, (3-6C)cycloalkenyl, (1-4C)alkylthio, amino, azido, cyano and nitro; or

(RTa2) (1-4C)alkylamino, di-(1-4C)alkylamino, and (2-4C)alkenylamino;

or RT is selected from the group

(RTb1) (1-4C)alkyl group which is optionally substituted by one substituent selected from hydroxy, (1-4C)alkoxy, (1-4C)alkylthio, cyano and azido; or

(RTb2) (1-4C)alkyl group which is optionally substituted by one substituent selected from (2-4C)alkenyloxy, (3-6C)cycloalkyl,and (3-6C)cycloalkenyl;

or RT is selected from the group

(RTc) a fully saturated 4-membered monocyclic ring containing 1 or 2 heteroatoms independently selected from O, N and S (optionally oxidised), and linked via a ring nitrogen or carbon atom;

and wherein at each occurrence of an RT substituent containing an alkyl, alkenyl, alkynyl, cycloalkyl or cycloalkenyl moiety in (RTa1) or (RTa2), (RTb1) or (RTb2), or (RTc) each such moiety is optionally substituted on an available carbon atom with one, two, three or more substituents independently selected from F, Cl, Br, OH and CN;

R_6 is cyano, $-COR_{12}$, $-COOR_{12}$, $-CONHR_{12}$, $-CON(R_{12})(R_{13})$, $-SO_2R_{12}$, $-SO_2NHR_{12}$,

$-SO_2N(R_{12})(R_{13})$ or NO_2, wherein R_{12} and R_{13} are as defined hereinbelow;

R_7 is hydrogen, amino, (1-8C)alkyl, $-NHR_{12}$, $-N(R_{12})(R_{13})$, $-OR_{12}$ or $-SR_{12}$, (2-4C)alkenyl, -(1-8C)alkylaryl, mono-, di-, tri- and per-halo(1-8C)alkyl, $-(CH_2)p$(3-6C)cycloalkyl or $-(CH_2)p$(3-6C)cycloalkenyl wherein p is 0, 1 or 2;

R_8 is hydrogen, (3-6C)cycloalkyl, phenyl, benzyl, (1-5C)alkanoyl, (1-6C)alkyl (optionally substituted by substituents independently selected from (1-5C)alkoxycarbonyl, hydroxy, cyano, up to 3 halogen atoms and $-NR_{15}R_{16}$ (wherein R_{15} and R_{16} are independently selected from hydrogen, phenyl (optionally substituted with one or more substituents selected from halogen, (1-4C)alkyl and (1-4C)alkyl substituted with one, two, three or more halogen atoms) and (1-4C)alkyl (optionally substituted with one, two, three or more halogen atoms), or for any $N(R_{15})(R_{16})$ group, R_{15} and R_{16} may additionally be taken together with the nitrogen atom to which they are attached to form a pyrrolidinyl, piperidinyl or morpholinyl ring);

R_9 and R_{10} are independently selected from hydrogen and (1-4C)alkyl;

R_{11} is (1-4C)alkyl or phenyl;

R_{12} and R_{13} are independently selected from hydrogen, phenyl (optionally substituted with one or more substituents selected from halogen, (1-4C)alkyl and (1-4C)alkyl substituted with one, two, three or more halogen atoms) and (1-4C)alkyl (optionally substituted with one, two, three or more halogen atoms), or for any $N(R_{12})(R_{13})$ group, R_{12} and R_{13} may additionally be taken together with the nitrogen atom to which they are attached to form a pyrrolidinyl, piperidinyl or morpholinyl ring, which ring may be optionally substituted by a group selected from (1-4C)alkyl, (1-4C)cycloalkyl, (1-4C)acyl, -COO(1-4C)alkyl, S(O)n(1-4C)alkyl (wherein n = 1 or 2), -COOAR1, -CS(1-4C)alkyl and –C(=S)O(1-4C)alkyl;

AR1 is an optionally substituted phenyl or optionally substituted naphthyl;

AR2 is an optionally substituted 5- or 6-membered, fully unsaturated (i.e with the maximum degree of unsaturation) monocyclic heteroaryl ring containing up to four heteroatoms independently selected from O, N and S (but not containing any O-O, O-S or S-S bonds), and linked via a ring carbon atom, or a ring nitrogen atom if the ring is not thereby quaternised;

AR2a is a partially hydrogenated version of AR2 (i.e. AR2 systems retaining some, but not the full, degree of unsaturation), linked via a ring carbon atom or linked via a ring nitrogen atom if the ring is not thereby quaternised;

AR2b is a fully hydrogenated version of AR2 (i.e. AR2 systems having no unsaturation), linked via a ring carbon atom or linked via a ring nitrogen atom;

AR3 is an optionally substituted 8-, 9- or 10-membered, fully unsaturated (i.e with the

maximum degree of unsaturation) bicyclic heteroaryl ring containing up to four heteroatoms independently selected from O, N and S (but not containing any O-O, O-S or S-S bonds), and linked via a ring carbon atom in either of the rings comprising the bicyclic system;

AR3a is a partially hydrogenated version of AR3 (i.e. AR3 systems retaining some, but not the full, degree of unsaturation), linked via a ring carbon atom, or linked via a ring nitrogen atom if the ring is not thereby quaternised, in either of the rings comprising the bicyclic system;

AR3b is a fully hydrogenated version of AR3 (i.e. AR3 systems having no unsaturation), linked via a ring carbon atom, or linked via a ring nitrogen atom, in either of the rings comprising the bicyclic system;

AR4 is an optionally substituted 13- or 14-membered, fully unsaturated (i.e with the maximum degree of unsaturation) tricyclic heteroaryl ring containing up to four heteroatoms independently selected from O, N and S (but not containing any O-O, O-S or S-S bonds), and linked via a ring carbon atom in any of the rings comprising the tricyclic system;

AR4a is a partially hydrogenated version of AR4 (i.e. AR4 systems retaining some, but not the full, degree of unsaturation), linked via a ring carbon atom, or linked via a ring nitrogen atom if the ring is not thereby quaternised, in any of the rings comprising the tricyclic system;

CY1 is an optionally substituted cyclobutyl, cyclopentyl or cyclohexyl ring;

CY2 is an optionally substituted cyclopentenyl or cyclohexenyl ring;

wherein; optional substituents on AR1, AR2, AR2a, AR2b, AR3, AR3a, AR3b, AR4, AR4a, CY1 and CY2 are (on an available carbon atom) up to three substituents independently selected from (1-4C)alkyl {optionally substituted by substituents selected independently from hydroxy, trifluoromethyl, (1-4C)alkyl S(O)q- (q is 0, 1 or 2), (1-4C)alkoxy, (1-4C)alkoxycarbonyl, cyano, nitro, (1-4C)alkanoylamino, -CONRvRw or -NRvRw}, trifluoromethyl, hydroxy, halo, nitro, cyano, thiol, (1-4C)alkoxy, (1-4C)alkanoyloxy, dimethylaminomethyleneaminocarbonyl, di(N-(1-4C)alkyl)aminomethylimino, carboxy, (1-4C)alkoxycarbonyl, (1-4C)alkanoyl, (1-4C)alkylSO_2amino, (2-4C)alkenyl {optionally substituted by carboxy or (1-4C)alkoxycarbonyl}, (2-4C)alkynyl, (1-4C)alkanoylamino, oxo (=O), thioxo (=S), (1-4C)alkanoylamino {the (1-4C)alkanoyl group being optionally substituted by hydroxy}, (1-4C)alkyl S(O)q- (q is 0, 1 or 2) {the (1-4C)alkyl group being optionally substituted by one or more groups independently selected from cyano, hydroxy and (1-4C)alkoxy}, -CONRvRw or -NRvRw [wherein Rv is hydrogen or (1-4C)alkyl; Rw is hydrogen or (1-4C)alkyl];

and further optional substituents on AR1, AR2, AR2a, AR2b, AR3, AR3a, AR3b, AR4, AR4a, CY1 and CY2 (on an available carbon atom), and also on alkyl groups (unless indicated otherwise) are up to three substituents independently selected from trifluoromethoxy, benzoylamino, benzoyl, phenyl {optionally substituted by up to three substituents independently selected from halo, (1-4C)alkoxy or cyano}, furan, pyrrole, pyrazole, imidazole, triazole, pyrimidine, pyridazine, pyridine, isoxazole, oxazole, isothiazole, thiazole, thiophene, hydroxyimino(1-4C)alkyl, (1-4C)alkoxyimino(1-4C)alkyl, halo-(1-4C)alkyl, (1-4C)alkanesulfonamido, $-SO_2NRvRw$ [wherein Rv is hydrogen or (1-4C)alkyl; Rw is hydrogen or (1-4C)alkyl]; and

optional substituents on AR2, AR2a, AR2b, AR3, AR3a, AR3b, AR4 and AR4a are (on an available nitrogen atom, where such substitution does not result in quaternization) (1-4C)alkyl, (1-4C)alkanoyl {wherein the (1-4C)alkyl and (1-4C)alkanoyl groups are optionally substituted by (preferably one) substituents independently selected from cyano, hydroxy, nitro, trifluoromethyl, (1-4C)alkyl S(O)q- (q is 0, 1 or 2), (1-4C)alkoxy, (1-4C)alkoxycarbonyl, (1-4C)alkanoylamino, -CONRvRw or -NRvRw [wherein Rv is hydrogen or (1-4C)alkyl; Rw is hydrogen or (1-4C)alkyl]}, (2-4C)alkenyl, (2-4C)alkynyl, (1-4C)alkoxycarbonyl or oxo (to form an N-oxide).

In this specification, HET-1A and HET-1B are fully unsaturated ring systems.

In this specification, HET-2A may be a fully or partially unsaturated heterocyclic ring, provided there is some degree of unsaturation in the ring.

Examples of 5-membered heteroaryl rings containing 2 to 4 heteroatoms independently selected from N, O and S (with no O-O, O-S or S-S bonds) are pyrazole, imidazole, 1,2,3-triazole, 1,2,4-triazole, oxazole, isoxazole, thiazole, 1,2,3-oxadiazole, 1,2,4-oxadiazole, 1,2,5-oxadiazole, 1,3,4-oxadiazole, isothiazole, 1,2,5-thiadiazole, 1,2,4-thiadiazole and 1,2,3-thiadiazole.

Examples of 6-membered heteroaryl ring systems containing up to three nitrogen heteroatoms are pyrimidine, pyridazine, pyrazine, 1,2,3-triazine, 1,2,4-triazine and 1,3,5-triazine.

Examples of N-linked 5-membered, fully or partially unsaturated heterocyclic rings, containing either (i) 1 to 3 further nitrogen heteroatoms or (ii) a further heteroatom selected from O and S together with an optional further nitrogen heteroatom include, for example,

pyrazole, imidazole, 1,2,3-triazole (preferably 1,2,3-triazol-1-yl), 1,2,4-triazole (preferably 1,2,4-triazol-1-yl), tetrazole (preferably tetrazol-2-yl) and furazan.

Examples of N-linked 6-membered di-hydro-heteroaryl rings containing up to three nitrogen heteroatoms in total (including the linking heteroatom) include di-hydro versions of pyrimidine, pyridazine, pyrazine, 1,2,3-triazine, 1,2,4-triazine, 1,3,5-triazine and pyridine.

Particular examples of halogen-substituted alkyl substituents in HET-1 and HET-2 are monofluoromethyl, difluoromethyl, chloromethyl, dichloromethyl and trifluoromethyl.

A particular example of R_8 as a halogen-substituted alkyl group is trifluoromethyl.

In this specification the term 'alkyl' includes straight chain and branched structures. For example, (1-4C)alkyl includes propyl and isopropyl. However, references to individual alkyl groups such as "propyl" are specific for the straight chain version only, and references to individual branched chain alkyl groups such as "isopropyl" are specific for the branched chain version only. A similar convention applies to other radicals, for example halo(1-4C)alkyl includes 1-bromoethyl and 2-bromoethyl.

In this specification, the terms 'alkenyl' and 'cycloalkenyl' include all positional and geometrical isomers.

In this specification, the term 'aryl' is an unsubstituted carbocyclic aromatic group, in particular phenyl, 1- and 2-naphthyl.

In this specification, where it is stated that a ring may be linked via an sp^2 carbon atom it is to be understood that the ring is linked via one of the carbon atoms in a C=C double bond.

For the avoidance of doubt, reference to a carbon atom in HET1 or HET2 being substituted by an oxo or thioxo group means replacement of a CH2 by C=O or C=S respectively.

There follow particular and suitable values for certain substituents and groups referred to in this specification. These values may be used where appropriate with any of the definitions and embodiments disclosed hereinbefore, or hereinafter. For the avoidance of doubt each stated species represents a particular and independent aspect of this invention.

Examples of **(1-4C)alkyl** and **(1-5C)alkyl** include methyl, ethyl, propyl, isopropyl and t-butyl; examples of **(1-6C)alkyl** include methyl, ethyl, propyl, isopropyl, t-butyl, pentyl and hexyl; examples of **(1-10C)alkyl** include methyl, ethyl, propyl, isopropyl, pentyl, hexyl, heptyl, octyl and nonyl; examples of **(1-4C)alkanoylamino-(1-4C)alkyl** include formamidomethyl, acetamidomethyl and acetamidoethyl; examples of **hydroxy(1-4C)alkyl** and **hydroxy(1-6C)alkyl** include hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl and

3-hydroxypropyl; examples of **(1-4C)alkoxycarbonyl** include methoxycarbonyl, ethoxycarbonyl and propoxycarbonyl; examples of **(1-5C)alkoxycarbonyl** include methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl and pentoxycarbonyl; examples of **2-((1-4C)alkoxycarbonyl)ethenyl** include 2-(methoxycarbonyl)ethenyl and 2-(ethoxycarbonyl)ethenyl; examples of **2-cyano-2-((1-4C)alkyl)ethenyl** include 2-cyano-2-methylethenyl and 2-cyano-2-ethylethenyl; examples of **2-nitro-2-((1-4C)alkyl)ethenyl** include 2-nitro-2-methylethenyl and 2-nitro-2-ethylethenyl; examples of **2-((1-4C)alkylaminocarbonyl)ethenyl** include 2-(methylaminocarbonyl)ethenyl and 2-(ethylaminocarbonyl)ethenyl; examples of **(2-4C)alkenyl** include allyl and vinyl; examples of **(2-4C)alkynyl** include ethynyl and 2-propynyl; examples of **(1-4C)alkanoyl** include formyl, acetyl and propionyl; examples of **(1-4C)alkoxy** include methoxy, ethoxy and propoxy; examples of **(1-6C)alkoxy** and **(1-10C)alkoxy** include methoxy, ethoxy, propoxy and pentoxy; examples of **(1-4C)alkylthio** include methylthio and ethylthio; examples of **(1-4C)alkylamino** include methylamino, ethylamino and propylamino; examples of **di-((1-4C)alkyl)amino** include dimethylamino, N-ethyl-N-methylamino, diethylamino, N-methyl-N-propylamino and dipropylamino; examples of **halo** groups include fluoro, chloro and bromo; examples of **(1-4C)alkylsulfonyl** include methylsulfonyl and ethylsulfonyl; examples of **(1-4C)alkoxy-(1-4C)alkoxy** and **(1-6C)alkoxy-(1-6C)alkoxy** include methoxymethoxy, 2-methoxyethoxy, 2-ethoxyethoxy and 3-methoxypropoxy; examples of **(1-4C)alkoxy-(1-4C)alkoxy-(1-4C)alkoxy** include 2-(methoxymethoxy)ethoxy, 2-(2-methoxyethoxy)ethoxy; 3-(2-methoxyethoxy)propoxy and 2-(2-ethoxyethoxy)ethoxy; examples of **(1-4C)alkylS(O)$_2$amino** include methylsulfonylamino and ethylsulfonylamino; examples of **(1-4C)alkanoylamino** and **(1-6C)alkanoylamino** include formamido, acetamido and propionylamino; examples of **(1-4C)alkoxycarbonylamino** include methoxycarbonylamino and ethoxycarbonylamino; examples of **N-(1-4C)alkyl-N-(1-6C)alkanoylamino** include N-methylacetamido, N-ethylacetamido and N-methylpropionamido; examples of **(1-4C)alkylS(O)$_p$NH-** wherein p is 1 or 2 include methylsulfinylamino, methylsulfonylamino, ethylsulfinylamino and ethylsulfonylamino; examples of **(1-4C)alkylS(O)$_p$((1-4C)alkyl)N-** wherein p is 1 or 2 include methylsulfinylmethylamino, methylsulfonylmethylamino, 2-(ethylsulfinyl)ethylamino and 2-(ethylsulfonyl)ethylamino; examples of **fluoro(1-4C)alkylS(O)$_p$NH-** wherein p is 1 or 2 include trifluoromethylsulfinylamino and trifluoromethylsulfonylamino; examples of **fluoro(1-4C)alkylS(O)$_p$((1-4C)alkyl)NH-** wherein p is 1 or 2 include

trifluoromethylsulfinylmethylamino and trifluoromethylsulfonylmethylamino examples of **(1-4C)alkoxy(hydroxy)phosphoryl** include methoxy(hydroxy)phosphoryl and ethoxy(hydroxy)phosphoryl; examples of **di-(1-4C)alkoxyphosphoryl** include di-methoxyphosphoryl, di-ethoxyphosphoryl and ethoxy(methoxy)phosphoryl; examples of **(1-4C)alkylS(O)$_q$-** wherein q is 0, 1 or 2 include methylthio, ethylthio, methylsulfinyl, ethylsulfinyl, methylsulfonyl and ethylsulfonyl; examples of **phenylS(O)q** and **naphthylS(O)$_q$-** wherein q is 0, 1 or 2 are phenylthio, phenylsulfinyl, phenylsulfonyl and naphthylthio, naphthylsulfinyl and naphthylsulfonyl respectively; examples of **benzyloxy-(1-4C)alkyl** include benzyloxymethyl and benzyloxyethyl; examples of a **(3-4C)alkylene** chain are trimethylene or tetramethylene; examples of **(1-6C)alkoxy-(1-6C)alkyl** include methoxymethyl, ethoxymethyl and 2-methoxyethyl; examples of **hydroxy-(2-6C)alkoxy** include 2-hydroxyethoxy and 3-hydroxypropoxy; examples of **(1-4C)alkylamino-(2-6C)alkoxy** include 2-methylaminoethoxy and 2-ethylaminoethoxy; examples of **di-(1-4C)alkylamino-(2-6C)alkoxy** include 2-dimethylaminoethoxy and 2-diethylaminoethoxy; examples of **-(1-8C)alkylaryl** include benzyl and phenethyl; examples of **(1-4C)alkylcarbamoyl** include methylcarbamoyl and ethylcarbamoyl; examples of **di((1-4C)alkyl)carbamoyl** include di(methyl)carbamoyl and di(ethyl)carbamoyl; examples of **hydroxyimino(1-4C)alkyl** include hydroxyiminomethyl, 2-(hydroxyimino)ethyl and 1-(hydroxyimino)ethyl; examples of **(1-4C)alkoxyimino-(1-4C)alkyl** include methoxyiminomethyl, ethoxyiminomethyl, 1-(methoxyimino)ethyl and 2-(methoxyimino)ethyl; examples of **halo(1-4C)alkyl** include, halomethyl, 1-haloethyl, 2-haloethyl, and 3-halopropyl; examples of **nitro(1-4C)alkyl** include nitromethyl, 1-nitroethyl, 2-nitroethyl and 3-nitropropyl; examples of **amino(1-4C)alkyl** include aminomethyl, 1-aminoethyl, 2-aminoethyl and 3-aminopropyl; examples of **cyano(1-4C)alkyl** include cyanomethyl, 1-cyanoethyl, 2-cyanoethyl and 3-cyanopropyl; examples of **(1-4C)alkanesulfonamido** include methanesulfonamido and ethanesulfonamido; examples of **(1-4C)alkylaminosulfonyl** include methylaminosulfonyl and ethylaminosulfonyl; and examples of **di-(1-4C)alkylaminosulfonyl** include dimethylaminosulfonyl, diethylaminosulfonyl and N-methyl-N-ethylaminosulfonyl; examples of **(1-4C)alkanesulfonyloxy** include methylsulfonyloxy, ethylsulfonyloxy and propylsulfonyloxy; examples of **(1-4C)alkanoyloxy** include acetoxy; examples of **(1-4C)alkylaminocarbonyl** include methylaminocarbonyl and ethylaminocarbonyl; examples of **di((1-4C)alkyl)aminocarbonyl** include dimethylaminocarbonyl and

diethylaminocarbonyl; examples of **(3-8C)cycloalkyl** include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl; examples of **(4-7C)cycloalkyl** include cyclobutyl, cyclopentyl and cyclohexyl; examples of **(3-6C)cycloalkenyl** include cyclopropenyl, cyclobutenyl, cyclopentenyl and cyclohexenyl; examples of **di(N-(1-4C)alkyl)aminomethylimino** include dimethylaminomethylimino and diethylaminomethylimino.

Particular values for AR2 include, for example, for those AR2 containing one heteroatom, furan, pyrrole, thiophene; for those AR2 containing one to four N atoms, pyrazole, imidazole, pyridine, pyrimidine, pyrazine, pyridazine, 1,2,3- & 1,2,4-triazole and tetrazole; for those AR2 containing one N and one O atom, oxazole, isoxazole and oxazine; for those AR2 containing one N and one S atom, thiazole and isothiazole; for those AR2 containing two N atoms and one S atom, 1,2,4- and 1,3,4-thiadiazole.

Particular examples of AR2a include, for example, dihydropyrrole (especially 2,5-dihydropyrrol-4-yl) and tetrahydropyridine (especially 1,2,5,6-tetrahydropyrid-4-yl).

Particular examples of AR2b include, for example, tetrahydrofuran, pyrrolidine, morpholine (preferably morpholino), thiomorpholine (preferably thiomorpholino), piperazine (preferably piperazino), imidazoline and piperidine, 1,3-dioxolan-4-yl, 1,3-dioxan-4-yl, 1,3-dioxan-5-yl and 1,4-dioxan-2-yl.

Particular values for AR3 include, for example, bicyclic benzo-fused systems containing a 5- or 6-membered heteroaryl ring containing one nitrogen atom and optionally 1-3 further heteroatoms chosen from oxygen, sulfur and nitrogen. Specific examples of such ring systems include, for example, indole, benzofuran, benzothiophene, benzimidazole, benzothiazole, benzisothiazole, benzoxazole, benzisoxazole, quinoline, quinoxaline, quinazoline, phthalazine and cinnoline.

Other particular examples of AR3 include 5/5-, 5/6 and 6/6 bicyclic ring systems containing heteroatoms in both of the rings. Specific examples of such ring systems include, for example, purine and naphthyridine.

Further particular examples of AR3 include bicyclic heteroaryl ring systems with at least one bridgehead nitrogen and optionally a further 1-3 heteroatoms chosen from oxygen, sulfur and nitrogen. Specific examples of such ring systems include, for example, 3H-pyrrolo[1,2-a]pyrrole, pyrrolo[2,1-b]thiazole, 1H-imidazo[1,2-a]pyrrole, 1H-imidazo[1,2-a]imidazole, 1H,3H-pyrrolo[1,2-c]oxazole, 1H-imidazo[1,5-a]pyrrole, pyrrolo[1,2-b]isoxazole, imidazo[5,1-b]thiazole, imidazo[2,1-b]thiazole, indolizine, imidazo[1,2-a]pyridine, imidazo[1,5-a]pyridine, pyrazolo[1,5-a]pyridine,

pyrrolo[1,2-b]pyridazine, pyrrolo[1,2-c]pyrimidine, pyrrolo[1,2-a]pyrazine, pyrrolo[1,2-a]pyrimidine, pyrido[2,1-c]-s-triazole, s-triazole[1,5-a]pyridine, imidazo[1,2-c]pyrimidine, imidazo[1,2-a]pyrazine, imidazo[1,2-a]pyrimidine, imidazo[1,5-a]pyrazine, imidazo[1,5-a]pyrimidine, imidazo[1,2-b]-pyridazine, s-triazolo[4,3-a]pyrimidine, imidazo[5,1-b]oxazole and imidazo[2,1-b]oxazole. Other specific examples of such ring systems include, for example, [1H]-pyrrolo[2,1-c]oxazine, [3H]-oxazolo[3,4-a]pyridine, [6H]-pyrrolo[2,1-c]oxazine and pyrido[2,1-c][1,4]oxazine. Other specific examples of 5/5- bicyclic ring systems are imidazooxazole or imidazothiazole, in particular imidazo[5,1-b]thiazole, imidazo[2,1-b]thiazole, imidazo[5,1-b]oxazole or imidazo[2,1-b]oxazole.

Particular examples of AR3a and AR3b include, for example, indoline, 1,3,4,6,9,9a-hexahydropyrido[2,1c][1,4]oxazin-8-yl, 1,2,3,5,8,8a-hexahydroimidazo[1,5a]pyridin-7-yl, 1,5,8,8a-tetrahydrooxazolo[3,4a]pyridin-7-yl, 1,5,6,7,8,8a-hexahydrooxazolo[3,4a]pyridin-7-yl, (7aS)[3H,5H]-1,7a-dihydropyrrolo[1,2c]oxazol-6-yl, (7aS)[5H]-1,2,3,7a-tetrahydropyrrolo[1,2c]imidazol-6-yl, (7aR)[3H,5H]-1,7a-dihydropyrrolo[1,2c]oxazol-6-yl, [3H,5H]-pyrrolo[1,2-c]oxazol-6-yl, [5H]-2,3-dihydropyrrolo[1,2-c]imidazol-6-yl, [3H,5H]-pyrrolo[1,2-c]thiazol-6-yl, [3H,5H]-1,7a-dihydropyrrolo[1,2-c]thiazol-6-yl, [5H]-pyrrolo[1,2-c]imidazol-6-yl, [1H]-3,4,8,8a-tetrahydropyrrolo[2,1-c]oxazin-7-yl, [3H]-1,5,8,8a-tetrahydrooxazolo-[3,4-a]pyrid-7-yl, [3H]-5,8-dihydroxazolo[3,4-a]pyrid-7-yl and 5,8-dihydroimidazo-[1,5-a]pyrid-7-yl.

Particular values for AR4 include, for example, pyrrolo[a]quinoline, 2,3-pyrroloisoquinoline, pyrrolo[a]isoquinoline, 1H-pyrrolo[1,2-a]benzimidazole, 9H-imidazo[1,2-a]indole, 5H-imidazo[2,1-a]isoindole, 1H-imidazo[3,4-a]indole, imidazo[1,2-a]quinoline, imidazo[2,1-a]isoquinoline, imidazo[1,5-a]quinoline and imidazo[5,1-a]isoquinoline.

The nomenclature used is that found in, for example, "Heterocyclic Compounds (Systems with bridgehead nitrogen), W.L.Mosby (Interscience Publishers Inc., New York), 1961, Parts 1 and 2.

Where optional substituents are listed such substitution is preferably not geminal disubstitution unless stated otherwise. If not stated elsewhere, suitable optional substituents for a particular group are those as stated for similar groups herein.

Preferable optional substituents on Ar2b as 1,3-dioxolan-4-yl, 1,3-dioxan-4-yl,

1,3-dioxan-5-yl or 1,4-dioxan-2-yl are mono- or disubstitution by substituents independently selected from (1-4C)alkyl (including geminal disubstitution), (1-4C)alkoxy, (1-4C)alkylthio, acetamido, (1-4C)alkanoyl, cyano, trifluoromethyl and phenyl].

Preferable optional substituents on CY1 & CY2 are mono- or disubstitution by substituents independently selected from (1-4C)alkyl (including geminal disubstitution), hydroxy, (1-4C)alkoxy, (1-4C)alkylthio, acetamido, (1-4C)alkanoyl, cyano, and trifluoromethyl.

Suitable pharmaceutically-acceptable salts include acid addition salts such as methanesulfonate, fumarate, hydrochloride, citrate, maleate, tartrate and (less preferably) hydrobromide. Also suitable are salts formed with phosphoric and sulfuric acid. In another aspect suitable salts are base salts such as an alkali metal salt for example sodium, an alkaline earth metal salt for example calcium or magnesium, an organic amine salt for example triethylamine, morpholine, N-methylpiperidine, N-ethylpiperidine, procaine, dibenzylamine, N,N-dibenzylethylamine, tris-(2-hydroxyethyl)amine, N-methyl d-glucamine and amino acids such as lysine. There may be more than one cation or anion depending on the number of charged functions and the valency of the cations or anions. A preferred pharmaceutically-acceptable salt is the sodium salt.

However, to facilitate isolation of the salt during preparation, salts which are less soluble in the chosen solvent may be preferred whether pharmaceutically-acceptable or not.

The compounds of the invention may be administered in the form of a pro-drug which is broken down in the human or animal body to give a compound of the invention. A prodrug may be used to alter or improve the physical and/or pharmacokinetic profile of the parent compound and can be formed when the parent compound contains a suitable group or substituent which can be derivatised to form a prodrug. Examples of pro-drugs include in-vivo hydrolysable esters of a compound of the invention or a pharmaceutically-acceptable salt thereof.

Various forms of prodrugs are known in the art, for examples see:

a) Design of Prodrugs, edited by H. Bundgaard, (Elsevier, 1985) and Methods in Enzymology, Vol. 42, p. 309-396, edited by K. Widder, *et al.* (Academic Press, 1985);

b) A Textbook of Drug Design and Development, edited by Krogsgaard-Larsen and H. Bundgaard, Chapter 5 "Design and Application of Prodrugs", by H. Bundgaard p. 113-191 (1991);

c) H. Bundgaard, Advanced Drug Delivery Reviews, 8, 1-38 (1992);

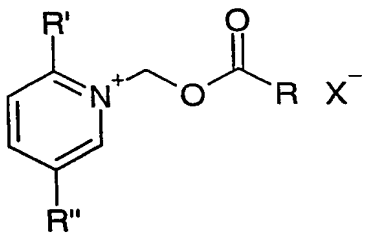
d) H. Bundgaard, *et al.*, Journal of Pharmaceutical Sciences, 77, 285 (1988); and

e) N. Kakeya, *et al.*, Chem Pharm Bull, 32, 692 (1984).

An in-vivo hydrolysable ester of a compound of the invention or a pharmaceutically-acceptable salt thereof containing a carboxy or hydroxy group is, for example, a pharmaceutically-acceptable ester which is hydrolysed in the human or animal body to produce the parent alcohol.

Suitable pharmaceutically-acceptable esters for carboxy include (1-6C)alkoxymethyl esters for example methoxymethyl, (1-6C)alkanoyloxymethyl esters for example pivaloyloxymethyl, phthalidyl esters, (3-8C)cycloalkoxycarbonyloxy(1-6C)alkyl esters for example 1-cyclohexylcarbonyloxyethyl; 1,3-dioxolan-2-onylmethyl esters for example 5-methyl-1,3-dioxolan-2-ylmethyl; and (1-6C)alkoxycarbonyloxyethyl esters for example 1-methoxycarbonyloxyethyl and may be formed at any carboxy group in the compounds of this invention.

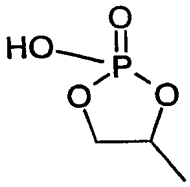
Further suitable pro-drugs for pyridine derivatives include acyloxymethyl pyridinium salts eg halides; for example a pro-drug such as:



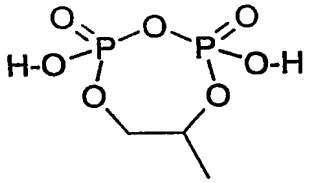
An in-vivo hydrolysable ester of a compound of the invention or a pharmaceutically-acceptable salt thereof containing a hydroxy group or groups includes inorganic esters such as phosphate esters (including phosphoramidic cyclic esters) and α-acyloxyalkyl ethers and related compounds which as a result of the in-vivo hydrolysis of the ester breakdown to give the parent hydroxy group/s. Examples of α-acyloxyalkyl ethers include acetoxymethoxy and 2,2-dimethylpropionyloxymethoxy. A selection of in-vivo hydrolysable ester forming groups for hydroxy include (1-10C)alkanoyl, benzoyl, phenylacetyl and substituted benzoyl and phenylacetyl, (1-10C)alkoxycarbonyl (to give alkyl carbonate esters), di-(1-4C)alkylcarbamoyl and N-(di-(1-4C)alkylaminoethyl)-N-(1-4C)alkylcarbamoyl (to give carbamates), di-(1-4C)alkylaminoacetyl, carboxy(2-5C)alkylcarbonyl and carboxyacetyl. Examples of ring substituents on phenylacetyl and benzoyl include chloromethyl or

aminomethyl, (1-4C)alkylaminomethyl and di-((1-4C)alkyl)aminomethyl, and morpholino or piperazino linked from a ring nitrogen atom via a methylene linking group to the 3- or 4-position of the benzoyl ring. Other interesting in-vivo hydrolysable esters include, for example, $R^A C(O)O(1\text{-}6C)alkyl\text{-}CO$- (wherein R^A is for example, optionally substituted benzyloxy-(1-4C)alkyl, or optionally substituted phenyl; suitable substituents on a phenyl group in such esters include, for example, 4-(1-4C)piperazino-(1-4C)alkyl, piperazino-(1-4C)alkyl and morpholino-(1-4C)alkyl.

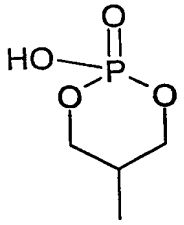
Suitable in-vivo hydrolysable esters of a compound of the formula (I) are described as follows. For example, a 1,2-diol may be cyclised to form a cyclic ester of formula (PD1) or a pyrophosphate of formula (PD2), and a 1,3-diol may be cyclised to form a cyclic ester of the formula (PD3):



(PD1)



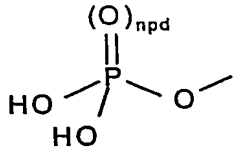
(PD2)



(PD3)

Esters of compounds of formula (I) wherein the HO- function/s in (PD1), (PD2) and (PD3) are protected by (1-4C)alkyl, phenyl or benzyl are useful intermediates for the preparation of such pro-drugs.

Further in-vivo hydrolysable esters include phosphoramidic esters, and also compounds of invention in which any free hydroxy group independently forms a phosphoryl (npd is 1) or phosphiryl (npd is 0) ester of the formula (PD4) :



(PD4)

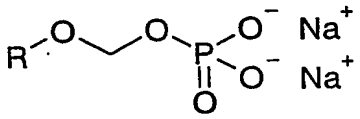
For the avoidance of doubt, phosphono is $-P(O)(OH)_2$; (1-4C)alkoxy(hydroxy)-phosphoryl is a mono-(1-4C)alkoxy derivative of $-O-P(O)(OH)_2$; and di-(1-4C)alkoxyphosphoryl is a di-(1-4C)alkoxy derivative of $-O-P(O)(OH)_2$.

Useful intermediates for the preparation of such esters include compounds containing a group/s of formula (PD4) in which either or both of the -OH groups in (PD1) is

independently protected by (1-4C)alkyl (such compounds also being interesting compounds in their own right), phenyl or phenyl-(1-4C)alkyl (such phenyl groups being optionally substituted by 1 or 2 groups independently selected from (1-4C)alkyl, nitro, halo and (1-4C)alkoxy).

Thus, prodrugs containing groups such as (PD1), (PD2), (PD3) and (PD4) may be prepared by reaction of a compound of invention containing suitable hydroxy group/s with a suitably protected phosphorylating agent (for example, containing a chloro or dialkylamino leaving group), followed by oxidation (if necessary) and deprotection.

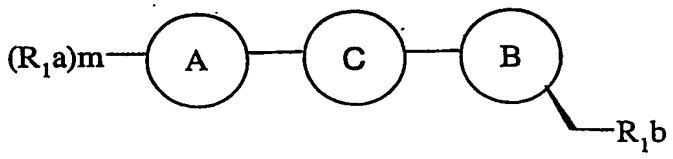
Other suitable prodrugs include phosphonooxymethyl ethers and their salts, for example a prodrug of R-OH such as:



When a compound of invention contains a number of free hydroxy group, those groups not being converted into a prodrug functionality may be protected (for example, using a t-butyl-dimethylsilyl group), and later deprotected. Also, enzymatic methods may be used to selectively phosphorylate or dephosphorylate alcohol functionalities.

Where pharmaceutically-acceptable salts of an in-vivo hydrolysable ester may be formed this is achieved by conventional techniques. Thus, for example, compounds containing a group of formula (PD1), (PD2), (PD3)and/or (PD4) may ionise (partially or fully) to form salts with an appropriate number of counter-ions. Thus, by way of example, if an in-vivo hydrolysable ester prodrug of a compound of invention contains two (PD4) groups, there are four HO-P- functionalities present in the overall molecule, each of which may form an appropriate salt (i.e. the overall molecule may form, for example, a mono-, di-, tri- or tetra-sodium salt).

The compounds of the present invention have a chiral centre at the C-5 position of the oxazolidinone or isoxazoline ring B. Where m>0 there may be additional chiral centres at C-4 and/or C-5 position of Ring A. The pharmaceutically active diastereomers are of the formula (IA):



(IA)

wherein the chiral centre of ring B is fixed in the orientation shown (generally the (5R) configuration, depending on the nature of R_1b, C and B) and ring B is acting as a pharmacophoric group; and wherein the substitution pattern and orientation of the chiral centre(s) at ring A may vary and may influence whether ring A also independently binds to a pharmacophore binding site.

Furthermore, some compounds of the invention may have other chiral centres. It is to be understood that the invention encompasses all such optical and diastereoisomers, and racemic mixtures, that possess antibacterial activity. It is well known in the art how to prepare optically-active forms (for example by resolution of the racemic form by recrystallisation techniques, by chiral synthesis, by enzymatic resolution, by biotransformation or by chromatographic separation) and how to determine antibacterial activity as described hereinafter.

The invention relates to all tautomeric forms of the compounds of the invention that possess antibacterial activity.

It is also to be understood that certain compounds of the invention can exist in solvated as well as unsolvated forms such as, for example, hydrated forms. It is to be understood that the invention encompasses all such solvated forms which possess antibacterial activity.

It is also to be understood that certain compounds of the invention may exhibit polymorphism, and that the invention encompasses all such forms which possess antibacterial activity.

As stated before, we have discovered a range of compounds that have good activity against a broad range of Gram-positive pathogens including organisms known to be resistant to most commonly used antibiotics, together with activity against fastidious Gram negative pathogens such as H.influenzae, M.catarrhalis, Mycoplasma and Chlamydia strains. The following compounds possess preferred pharmaceutical and/or physical and/or pharmacokinetic properties.

In one embodiment of the invention are provided compounds of formula (I), in an

alternative embodiment are provided pharmaceutically-acceptable salts of compounds of formula (I), in a further alternative embodiment are provided in-vivo hydrolysable esters of compounds of formula (I), and in a further alternative embodiment are provided pharmaceutically-acceptable salts of in-vivo hydrolysable esters of compounds of formula (I).

In one aspect, an in-vivo hydrolysable ester of a compound of the formula (I) is a phosphoryl ester (as defined by formula (PD4) with npd as 1).

Compounds of the formula (I), or a pharmaceutically-acceptable salt or an in-vivo hydrolysable ester thereof, wherein C is selected from any one of groups D to O represent separate and independent aspects of the invention.

Particularly preferred compounds of the invention comprise a compound of the invention, or a pharmaceutically-acceptable salt or an in-vivo hydrolysable ester thereof, wherein the substituents A, B, R_1a, R_1b, R_2a, R_2b, R_3a, R_3b R_5a, R_5a', R_6a and $R_6a'$and other substituents mentioned above have values disclosed hereinbefore, or any of the following values (which may be used where appropriate with any of the definitions and embodiments disclosed hereinbefore or hereinafter):

In one embodiment are provided compounds as defined herein in formula (I) or a pharmaceutically-acceptable salt or an in-vivo hydrolysable ester thereof, in which group C is group D.

In another embodiment are provided compounds as defined herein in formula (I) or a pharmaceutically-acceptable salt or an in-vivo hydrolysable ester thereof, in which group C is group E.

In another embodiment are provided compounds as defined herein in formula (I) or a pharmaceutically-acceptable salt or an in-vivo hydrolysable ester thereof, in which group C is group F.

In another embodiment are provided compounds as defined herein in formula (I) or a pharmaceutically-acceptable salt or an in-vivo hydrolysable ester thereof, in which group C is group G.

In another embodiment are provided compounds as defined herein in formula (I) or a pharmaceutically-acceptable salt or an in-vivo hydrolysable ester thereof, in which group C is group H.

In another embodiment are provided compounds as defined herein in formula (I) or a pharmaceutically-acceptable salt or an in-vivo hydrolysable ester thereof, in which group C is group I.

In another embodiment are provided compounds as defined herein in formula (I) or a pharmaceutically-acceptable salt or an in-vivo hydrolysable ester thereof, in which group C is group J.

In another embodiment are provided compounds as defined herein in formula (I) or a pharmaceutically-acceptable salt or an in-vivo hydrolysable ester thereof, in which group C is group K.

In another embodiment are provided compounds as defined herein in formula (I) or a pharmaceutically-acceptable salt or an in-vivo hydrolysable ester thereof, in which group C is group L.

In another embodiment are provided compounds as defined herein in formula (I) or a pharmaceutically-acceptable salt or an in-vivo hydrolysable ester thereof, in which group C is group M.

In another embodiment are provided compounds as defined herein in formula (I) or a pharmaceutically-acceptable salt or an in-vivo hydrolysable ester thereof, in which group C is group N.

In another embodiment are provided compounds as defined herein in formula (I) or a pharmaceutically-acceptable salt or an in-vivo hydrolysable ester thereof, in which group C is group O.

In another embodiment are provided compounds of formula (I) or a pharmaceutically-acceptable salt or an in-vivo hydrolysable ester thereof, in which group C is a group selected from groups D, E, H and I as hereinbefore defined.

In a further embodiment are provided compounds of formula (I) or a pharmaceutically-acceptable salt or an in-vivo hydrolysable ester thereof, in which group C is a group selected from groups D and E as hereinbefore defined.

In a further embodiment are provided compounds of formula (I) or a pharmaceutically-acceptable salt or an in-vivo hydrolysable ester thereof, in which group C is a group selected from groups D and H as hereinbefore defined.

In one aspect both A and B are oxazolidinone rings.

In another aspect, either A or B is an oxazolidinone ring and the other is an isoxazoline ring.

In a further aspect both A and B are isoxazoline rings.

In one aspect, R_2b and R_6b are independently H or F.

In one aspect R_2b' and R_6b' are both H.

When m = 1, in one aspect R_1a is selected from R_1a1; in another aspect R_1a is selected from R_1a2; in a further aspect R_1a is selected from R_1a3 and in a further aspect R_1a is selected from R_1a4.

When m = 2, in one aspect both groups R_1a are independently selected from the same group R_1a1 to R_1a4. In a further aspect when m = 2, each R_1a is independently selected from different groups R_1a1 to R_1a4.

Conveniently, m is 1 or 2. In one embodiment preferably m is 1. In another embodiment, preferably m is 2.

In one aspect, when m is 2, both substituents R_1a are attached to position 4 of ring A and joined together to form a 5-7 membered spiro-ring.

In one aspect, when m is 2, both substituents R_1a are attached to position 5 of ring A and joined together to form a 5-7 membered spiro-ring.

In another aspect, when m is 2, one substituent R_1a is attached to position 4 of ring A, and the other is attached to position 5 of ring A, such that taken together with A they form a 5-7 membered fused-ring.

In a particular aspect when m is 2, the two substituents R_1a are identical to each other, preferably selected from R_1a3 and are attached to the same position (4 or 5) of ring A such that ring A does not have a chiral centre.

Particular values for R_1a when selected from R_1a1 are AR1 and AR2, more particularly AR2.

Particular values for R_1a when selected from R_1a2 are cyano and -C(=W)NRvRw [wherein W is O or S, Rv and Rw are independently H, or (1-4C)alkyl and wherein Rv and Rw taken together with the amide or thioamide nitrogen to which they are attached can form a 5-7 membered ring optionally with an additional heteroatom selected from N, O, S(O)n in place of 1 carbon atom of the so formed ring; wherein when said ring is a piperazine ring, the ring may be optionally substituted on the additional nitrogen by a group selected from (1-4C)alkyl (optionally substituted on a carbon not adjacent to the nitrogen), (1-4C)cycloalkyl, (1-4C)acyl, -COO(1-4C)alkyl, S(O)n(1-4C)alkyl (wherein n = 1 or 2;), -COOAR1, -CS(1-4C)alkyl and –C(=S)O(1-4C)alkyl; wherein any (1-4C)alkyl, (1-4C)acyl and (1-4C)cycloalkyl is optionally substituted by cyano, hydroxy or halo]. More particular values for R_1a when selected from R_1a2 are cyano, formyl, -COO(1-4C)alkyl, -C(=O)NH_2, -(C=O)piperazine and -(C=O)morpholine.

Particular values for R_1a when selected from R_1a3 are (1-10C)alkyl {optionally substituted by one or more groups (including geminal disubstitution) each independently selected from hydroxy, (1-10C)alkoxy, (1-4C)alkoxy-(1-4C)alkoxy, (1-4C)alkoxy-(1-4C)alkoxy-(1-4C)alkoxy, (1-4C)alkylcarbonyl, phosphoryl [-O-P(O)$(OH)_2$, and mono- and di-(1-4C)alkoxy derivatives thereof], phosphiryl [-O-P$(OH)_2$ and mono- and di-(1-4C)alkoxy derivatives thereof], and amino; and/or optionally substituted by one group selected from carboxy, cyano, halo, trifluoromethyl, (1-4C)alkoxycarbonyl, (1-4C)alkoxy-(1-4C)alkoxycarbonyl, (1-4C)alkoxy-(1-4C)alkoxy-(1-4C)alkoxycarbonyl, (1-4C)alkylamino, di((1-4C)alkyl)amino, (1-6C)alkanoylamino-, (1-4C)alkoxycarbonylamino-, N-(1-4C)alkyl-N-(1-6C)alkanoylamino-, -C(=W)NRvRw [wherein W is O, Rv and Rw are independently H, or (1-4C)alkyl and wherein Rv and Rw taken together with the amide nitrogen to which they are attached can form a morpholine, pyrrolidine, piperidine or piperazine ring; wherein when said ring is a piperazine ring, the ring may be optionally substituted on the additional nitrogen by a group selected from (1-4C)alkyl and (1-4C)acyl], (1-4C)alkylS(O)q-, (q is 0, 1 or 2), AR2, AR2-O-, AR2-NH-, and also AR2a, AR2b versions of AR2 containing groups}; wherein any (1-4C)alkyl and (1-4C)acyl present in any substituent on R_1a3 may itself be substituted by one or two groups independently selected from cyano, hydroxy, halo, amino, (1-4C)alkylamino and di(1-4C)alkylamino, provided that such a substituent is not on a carbon adjacent to a heteroatom atom if present;

More particular values for R_1a when selected from R_1a3 are (1-10C)alkyl {optionally substituted by one or more groups (including geminal disubstitution) each independently selected from hydroxy, (1-10C)alkoxy, (1-4C)alkoxy-(1-4C)alkoxy, (1-4C)alkoxy-(1-4C)alkoxy-(1-4C)alkoxy, phosphoryl [-O-P(O)$(OH)_2$, and mono- and di-(1-4C)alkoxy derivatives thereof], phosphiryl [-O-P$(OH)_2$ and mono- and di-(1-4C)alkoxy derivatives thereof], carboxy, amino, (1-4C)alkylamino, di(1-4C)alkylamino, (1-4C)alkylS(O)q (preferably where q=2), AR2 and AR2b . More particular values for R_1a when selected from R_1a3 are (1-6C)alkyl substituted as hereinbefore described. Even more particular values for R_1a when selected from R_1a3 are (1-4C)alkyl substituted as hereinbefore described.

Particular values for R_1a when selected from R_1a4 are $R^{14}C(O)O(1\text{-}6C)alkyl$- wherein R^{14} is selected from AR1, AR2, AR2a,AR2b and (1-10C)alkyl (optionally substituted by one or more substituents independently selected from OH and di (1-4C)alkylamino. More particular vales for R^{14} are AR2a, AR2b and (1-6C)alkyl substituted with hydroxy. More particular values for R^{14} are AR2a, AR2b and (1-4C)alkyl substituted with hydroxy.

Particular values for R_1a when selected from R_1a5 are fluoro, chloro and hydroxy.

In all of the embodiments, aspects and preferable values for R_1b defined hereinbefore or hereinafter, any (1-4C)alkyl group may be optionally substituted as hereinbefore defined. Particular substituents for (1-4C)alkyl groups in definitions for R_1b are one or two halogen groups, particularly geminal disubstitution (provided that such substitution is not on a carbon atom attached to an oxygen) and cyano. Examples of di-halosubstituted groups are $-NHCOCF_2H$ and $-NHCSCCl_2H$.

When R_1b is $-N(R_5)$HET-1, R_5 is preferably hydrogen.

In one embodiment R_1b is selected from hydroxy, -NHCO(1-4C)alkyl, -NHCO(1-4C)cycloalkyl, -NHCS(1-4C)alkyl, -NHCOO(1-4C)alkyl, -NH(C=S)O(1-4C)alkyl, -OCO(1-4C)alkyl, $-N(R_5)$-HET-1 and HET-2.

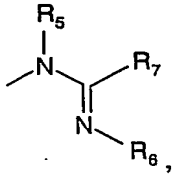
In another embodiment R_1b is selected from -NHCO(1-4C)alkyl, -NHCO(1-4C)cycloalkyl , -NHCS(1-4C)alkyl, $-N(R_5)$-HET-1 and HET-2.

More preferably R_1b is selected from -NHCO(1-4C)alkyl, -NHCS(1-4C)alkyl, $-N(R_5)$-HET-1 and HET-2.

In one aspect, R_1b is selected from OH, $-NR_5C(=W)R_4$ and $-OC(=O)R_4$, in particular OH, -NHCOMe and –NHCOOMe.

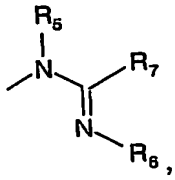
In a further aspect, R_1b is selected from $-N(R_5)$-HET-1 and HET-2, in particular HET-1 as isoxazolyl, 1,2,5-thiadiazolyl or isothiazolyl and HET-2 as 1,2,3-triazol-1-yl (optionally substituted) or tetrazol-2-yl.

In one embodiment R_1b is selected from hydroxy, $-NHC(=W)R_4$, $-OC(=O)R_4$, and



wherein W, R_5 and R_6 are as defined hereinbefore, R_4 is selected from hydrogen, amino, (1-4C)alkyl, -NH(1-4C)alkyl, -N(di-(1-4C)alkyl), -O(1-4C)alkyl, -S(1-4C)alkyl, (2-4C)alkenyl, $-(CH_2)p$(3-6C)cycloalkyl and $-(CH_2)p$(3-6C)cycloalkenyl wherein p is 0, 1 or 2; and R_7 is selected from hydrogen, (1-8C)alkyl, $-OR_{12}$, $-SR_{12}$, amino, NHR_{12}, $N(R_{12})(R_{13})$, (1-8C)alkylaryl and mono-, di-, tri- and per-halo(1-8C)alkyl.

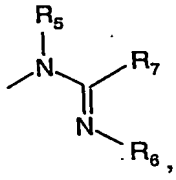
In another embodiment, R_1b is selected from hydroxy, $-NHC(=W)R_4$, $-OC(=O)R_4$,



and

wherein W, R_4, R_5, R_6 and R_7 are as defined hereinbefore, especially wherein R_4 is (1-4C)alkyl, (1-4C)alkoxy, cycloalkyl (particularly cyclopropyl) or haloalkyl (particularly dichloromethyl).

In another embodiment, R_1b is selected from hydroxy, -NHC(=W)R_4, -OC(=O)R_4,



and

wherein W, R_4, R_5, R_6 and R_7 are as defined hereinbefore, especially wherein R_4 is (1-4C)alkyl or (1-4C)alkoxy.

Particular values for R_5 (which may be used as appropriate with any of the definitions and embodiments disclosed hereinbefore or hereinafter) are hydrogen, tert-butoxycarbonyl and benzyloxycarbonyl. More particularly, R_5 is hydrogen.

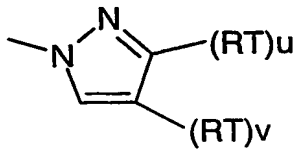
In one aspect R_{12} and R_{13} are independently selected from hydrogen, alkyl and aryl, or for any N(R_{12})(R_{13}) group, R_{12} and R_{13} may additionally be taken together with the nitrogen atom to which they are attached to forma pyrrolidinyl, piperidinyl or morpholinyl group, optionally substituted as hereinbefore described. In one aspect R_{15} and R_{16} are independently selected from hydrogen, phenyl and (1-4C)alkyl).

In one embodiment HET-1 and HET-2 are unsubstituted. When substituted, preferred substituents are selected from halo (particularly chloro), (1-4C)alkyl, especially methyl, mono- and di-halo methyl (wherein halo is preferably fluoro, chloro or bromo), trifluoromethyl and cyanomethyl.

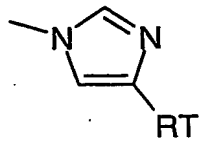
Preferred are HET-1 and HET-2 as 5-membered rings, ie HET-1 as HET-1A and HET_2 as HET-2A, in particular HET-1A as isoxazolyl, 1,2,5-thiadiazolyl or isothiazolyl and HET-2A as 1,2,3-triazol-1-yl or tetrazol-2-yl.

In one aspect, HET-2A as 1,2,3-triazol-1-yl is substituted, preferably by halo (particularly chloro), methyl, difluoromethyl, fluoromethyl, chloromethyl, cyanomethyl or trifluoromethyl.

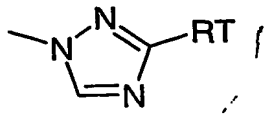
In one embodiment HET-2A is selected from the structures (Za) to (Zf) below:



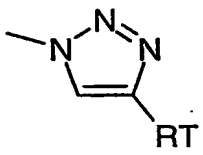
(Za)



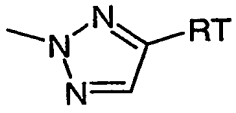
(Zb)



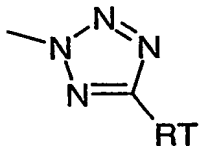
(Zc)



(Zd)



(Ze)



(Zf)

wherein u and v are independently 0 or 1 and RT is as defined in any of the embodiments or aspects defined hereinbefore or hereinafter.

In one embodiment HET-2A is selected from 1,2,3-triazole (especially 1,2,3-triazol-1-yl (Zd)), 1,2,4-triazole (especially 1,2,4-triazol-1-yl (Zc)) and tetrazole (preferably tetrazol-2-yl (Zf)) and wherein u and v are independently 0 or 1 and RT is as defined in any of the embodiments or aspects defined hereinbefore or hereinafter.

In another embodiment HET-2A is selected from 1,2,3-triazol-1-yl (Zd) and tetrazol-2-yl (Zf) and wherein u and v are independently 0 or 1 and RT is as defined in any of the embodiments or aspects defined hereinbefore or hereinafter.

In another embodiment HET-2A is 1,2,3-triazol-1-yl (Zd) and wherein u and v are independently 0 or 1 and RT is as defined in any of the embodiments or aspects defined hereinbefore or hereinafter.

In one embodiment HET-2B is a di-hydro version of pyrimidine, pyridazine, pyrazine, 1,2,3-triazine, 1,2,4-triazine, 1,3,5-triazine and pyridine and wherein RT is as defined in any of the embodiments or aspects defined hereinbefore or hereinafter.

In another embodiment HET-2B is selected from pyrimidone, pyridazinone, pyrazinone, 1,2,3-triazinone, 1,2,4-triazinone, 1,3,5-triazinone and pyridone and wherein RT is as defined in any of the embodiments or aspects defined hereinbefore or hereinafter.

In another embodiment HET-2B is selected from thiopyrimidone, thiopyridazinone, thiopyrazinone, thio-1,2,3-triazinone, thio-1,2,4-triazinone, thio-1,3,5-triazinone and thiopyridone and wherein RT is as defined in any of the embodiments or aspects defined hereinbefore or hereinafter.

In one aspect RT is preferably selected from a substituent from the group

(RTa1) hydrogen, halogen, (1-4C)alkoxy, (2-4C)alkenyloxy, (2-4C)alkenyl, (2-4C)alkynyl, (3-6C)cycloalkyl, (3-6C)cycloalkenyl, (1-4C)alkylthio, amino, azido, cyano and nitro;or,

(RTa2) (1-4C)alkylamino, di-(1-4C)alkylamino and (2-4C)alkenylamino;

(RTb1) a (1-4C)alkyl group which is optionally substituted by one substituent selected from hydroxy, (1-4C)alkoxy, (1-4C)alkylthio, cyano and azido; or

(RTb2) a (1-4C)alkyl group which is optionally substituted by one substituent selected from (2-4C)alkenyloxy, (3-6C)cycloalkyl and (3-6C)cycloalkenyl;

and wherein at each occurrence of an RT substituent containing an alkyl, alkenyl, alkynyl, cycloalkyl or cycloalkenyl moiety in (RTa1) or (RTa2), or (RTb1) or (RTb2) each such moiety is optionally substituted on an available carbon atom with one, two, three or more substituents independently selected from F, Cl, Br, OH and CN.

In another aspect RT is preferably selected from a substituent from the group:

(RTa1) hydrogen, halogen, (1-4C)alkoxy, (2-4C)alkenyloxy, (2-4C)alkenyl, (2-4C)alkynyl, (3-6C)cycloalkyl, (3-6C)cycloalkenyl, (1-4C)alkylthio, amino, azido, cyano, and nitro; or

(RTb1) a (1-4C)alkyl group which is optionally substituted by one substituent selected from hydroxy, (1-4C)alkoxy, (1-4C)alkylthio, cyano and azido;

and wherein at each occurrence of an RT substituent containing an alkyl, alkenyl, alkynyl, cycloalkyl or cycloalkenyl moiety in (RTa1) or (RTb1) each such moiety is optionally substituted on an available carbon atom with one, two, three or more substituents independently selected from F, Cl, Br, and CN.

In a further aspect RT is most preferably

(a) hydrogen; or

(b) halogen, in particular fluorine, chlorine, or bromine; or

(c) cyano; or

(d) (1-4C)alkyl, in particular methyl; or

(e) monosubstituted (1-4C)alkyl, in particular fluoromethyl, choromethyl, bromomethyl, cyanomethyl, azidomethyl, hydroxymethyl; or

(f) disubstituted (1-4C)alkyl, for example difluoromethyl, or trisubstituted (1-4C)alkyl, for example trifluoromethyl.

In one embodiment is provided a compound of formula (I) or a pharmaceutically-acceptable salt or an in-vivo hydrolysable ester thereof, wherein group C is selected from groups D, E and H; R_2b and R_6b are independently H or F; A and B are both oxazolidinones; m = 0; and R_1b is selected from OH, -NHCOMe, -NHCOcyclopropyl, -NH(C=S)OMe and -NHCOOMe.

In one embodiment is provided a compound of formula (I) or a pharmaceutically-acceptable salt or an in-vivo hydrolysable ester thereof, wherein group C is selected from groups D, E and H; R_2b and R_6b are independently H or F; A and B are both oxazolidinones; m = 0; and R_1b is selected from -N(R_5)-HET-1A and HET-2A, in particular HET-1A as isoxazolyl, 1,2,5-thiadiazolyl or isothiazolyl and HET-2A as 1,2,3-triazol-1-yl (optionally substituted) or tetrazol-2-yl.

In one embodiment is provided a compound of formula (I) or a pharmaceutically-acceptable salt or an in-vivo hydrolysable ester thereof, wherein group C is selected from groups D, E and H; R_2b and R_6b are independently H or F; A and B are both isoxazolines; m = 0; and R_1b is selected from OH, -NHCOMe, -NHCOcyclopropyl, -NH(C=S)OMe and -NHCOOMe.

In one embodiment is provided a compound of formula (I) or a pharmaceutically-acceptable salt or an in-vivo hydrolysable ester thereof, wherein group C is selected from groups D, E and H; R_2b and R_6b are independently H or F; A and B are both isoxazolines; m = 0; and R_1b is selected from -N(R_5)-HET-1A and HET-2A, in particular HET-1A as isoxazolyl, 1,2,5-thiadiazolyl or isothiazolyl and HET-2A as 1,2,3-triazol-1-yl (optionally substituted) or tetrazol-2-yl.

In one embodiment is provided a compound of formula (I) or a pharmaceutically-acceptable salt or an in-vivo hydrolysable ester thereof, wherein group C is selected from groups D, E and H; R_2b and R_6b are independently H or F; either A or B is an oxazolidinone and the other is an isoxazoline; m = 0; and R_1b is selected from OH, -NHCOMe, -NHCOcyclopropyl, -NH(C=S)OMe and -NHCOOMe.

In one embodiment is provided a compound of formula (I) or a pharmaceutically-acceptable salt or an in-vivo hydrolysable ester thereof, wherein group C is selected from groups D, E and H; R_2b and R_6b are independently H or F; either A or B is an oxazolidinone and the other is an isoxazoline; m = 0; and R_1b is selected from -N(R_5)-HET-1A and HET-2A, in particular HET-1A as isoxazolyl, 1,2,5-thiadiazolyl or isothiazolyl and HET-2A as 1,2,3-triazol-1-yl (optionally substituted) or tetrazol-2-yl.

In one embodiment is provided a compound of formula (I) or a pharmaceutically-acceptable salt or an in-vivo hydrolysable ester thereof, wherein group C is selected from groups D, E and H; R_2b and R_6b are independently H or F; A and B are both oxazolidinones; m = 1; R_1a is selected from R_1a1; and R_1b is selected from OH, -NHCOMe, -NHCOcyclopropyl, -NH(C=S)OMe and -NHCOOMe.

In one embodiment is provided a compound of formula (I) or a pharmaceutically-acceptable salt or an in-vivo hydrolysable ester thereof, wherein group C is selected from groups D, E and H; R_2b and R_6b are independently H or F; A and B are both oxazolidinones; m = 1; R_1a is selected from R_1a1; and R_1b is selected from -N(R_5)-HET-1A and HET-2A, in particular HET-1A as isoxazolyl, 1,2,5-thiadiazolyl or isothiazolyl and HET-2A as 1,2,3-triazol-1-yl (optionally substituted) or tetrazol-2-yl.

In one embodiment is provided a compound of formula (I) or a pharmaceutically-acceptable salt or an in-vivo hydrolysable ester thereof, wherein group C is selected from groups D, E and H; R_2b and R_6b are independently H or F; A and B are both isoxazolines; m = 1; R_1a is selected from R_1a1; and R_1b is selected from OH, -NHCOMe, -NHCOcyclopropyl, -NH(C=S)OMe and -NHCOOMe.

In one embodiment is provided a compound of formula (I) or a pharmaceutically-acceptable salt or an in-vivo hydrolysable ester thereof, wherein group C is selected from groups D, E and H; R_2b and R_6b are independently H or F; A and B are both isoxazolines; m = 1; R_1a is selected from R_1a1; and R_1b is selected from -N(R_5)-HET-1A and HET-2A, in particular HET-1A as isoxazolyl, 1,2,5-thiadiazolyl or isothiazolyl and HET-2A as 1,2,3-triazol-1-yl (optionally substituted) or tetrazol-2-yl.

In one embodiment is provided a compound of formula (I) or a pharmaceutically-acceptable salt or an in-vivo hydrolysable ester thereof, wherein group C is selected from groups D, E and H; R_2b and R_6b are independently H or F; either A or B is an oxazolidinone and the other is an isoxazoline; m = 1; R_1a is selected from R_1a1; and R_1b is selected from OH, -NHCOMe, -NHCOcyclopropyl, -NH(C=S)OMe and -NHCOOMe.

In one embodiment is provided a compound of formula (I) or a pharmaceutically-acceptable salt or an in-vivo hydrolysable ester thereof, wherein group C is selected from groups D, E and H; R_2b and R_6b are independently H or F; either A or B is an oxazolidinone and the other is an isoxazoline; m = 1; R_1a is selected from R_1a1; and R_1b is selected from -N(R_5)-HET-1A and HET-2A, in particular HET-1A as isoxazolyl, 1,2,5-thiadiazolyl or isothiazolyl and HET-2A as 1,2,3-triazol-1-yl (optionally substituted) or tetrazol-2-yl.

In one embodiment is provided a compound of formula (I) or a pharmaceutically-acceptable salt or an in-vivo hydrolysable ester thereof, wherein group C is selected from groups D, E and H; R_2b and R_6b are independently H or F; A and B are both oxazolidinones; m = 1; R_1a is selected from R_1a2; and R_1b is selected from OH, -NHCOMe, -NHCOcyclopropyl, -NH(C=S)OMe and -NHCOOMe.

In one embodiment is provided a compound of formula (I) or a pharmaceutically-acceptable salt or an in-vivo hydrolysable ester thereof, wherein group C is selected from groups D, E and H; R_2b and R_6b are independently H or F; A and B are both oxazolidinones; m = 1; R_1a is selected from R_1a2; and R_1b is selected from -N(R_5)-HET-1A and HET-2A, in particular HET-1A as isoxazolyl, 1,2,5-thiadiazolyl or isothiazolyl and HET-2A as 1,2,3-triazol-1-yl (optionally substituted) or tetrazol-2-yl.

In one embodiment is provided a compound of formula (I) or a pharmaceutically-acceptable salt or an in-vivo hydrolysable ester thereof, wherein group C is selected from groups D, E and H; R_2b and R_6b are independently H or F; A and B are both isoxazolines; m = 1; R_1a is selected from R_1a2; and R_1b is selected from OH, -NHCOMe, -NHCOcyclopropyl, -NH(C=S)OMe and -NHCOOMe.

In one embodiment is provided a compound of formula (I) or a pharmaceutically-acceptable salt or an in-vivo hydrolysable ester thereof, wherein group C is selected from groups D, E and H; R_2b and R_6b are independently H or F; A and B are both isoxazolines; m = 1; R_1a is selected from R_1a2; and R_1b is selected from -N(R_5)-HET-1A and HET-2A, in particular HET-1A as isoxazolyl, 1,2,5-thiadiazolyl or isothiazolyl and HET-2A as 1,2,3-triazol-1-yl (optionally substituted) or tetrazol-2-yl.

In one embodiment is provided a compound of formula (I) or a pharmaceutically-acceptable salt or an in-vivo hydrolysable ester thereof, wherein group C is selected from groups D, E and H; R_2b and R_6b are independently H or F; either A or B is an oxazolidinone and the other is an isoxazoline; m = 1; R_1a is selected from R_1a2; and R_1b is selected from OH, -NHCOMe, -NHCOcyclopropyl, -NH(C=S)OMe and -NHCOOMe.

In one embodiment is provided a compound of formula (I) or a pharmaceutically-acceptable salt or an in-vivo hydrolysable ester thereof, wherein group C is selected from groups D, E and H; R_2b and R_6b are independently H or F; either A or B is an oxazolidinone and the other is an isoxazoline; m = 1; R_1a is selected from R_1a2; and R_1b is selected from -N(R_5)-HET-1A and HET-2A, in particular HET-1A as isoxazolyl, 1,2,5-thiadiazolyl or isothiazolyl and HET-2A as 1,2,3-triazol-1-yl (optionally substituted) or tetrazol-2-yl.

In one embodiment is provided a compound of formula (I) or a pharmaceutically-acceptable salt or an in-vivo hydrolysable ester thereof, wherein group C is selected from groups D, E and H; R_2b and R_6b are independently H or F; A and B are both oxazolidinones; m = 1; R_1a is selected from R_1a3; and R_1b is selected from OH, -NHCOMe, -NHCOcyclopropyl, -NH(C=S)OMe and -NHCOOMe.

In one embodiment is provided a compound of formula (I) or a pharmaceutically-acceptable salt or an in-vivo hydrolysable ester thereof, wherein group C is selected from groups D, E and H; R_2b and R_6b are independently H or F; A and B are both oxazolidinones; m = 1; R_1a is selected from R_1a3; and R_1b is selected from -N(R_5)-HET-1A and HET-2A, in particular HET-1A as isoxazolyl, 1,2,5-thiadiazolyl or isothiazolyl and HET-2A as 1,2,3-triazol-1-yl (optionally substituted) or tetrazol-2-yl.

In one embodiment is provided a compound of formula (I) or a pharmaceutically-acceptable salt or an in-vivo hydrolysable ester thereof, wherein group C is selected from groups D, E and H; R_2b and R_6b are independently H or F; A and B are both isoxazolines; m = 1; R_1a is selected from R_1a3; and R_1b is selected from OH, -NHCOMe, -NHCOcyclopropyl, -NH(C=S)OMe and -NHCOOMe.

In one embodiment is provided a compound of formula (I) or a pharmaceutically-acceptable salt or an in-vivo hydrolysable ester thereof, wherein group C is selected from groups D, E and H; R_2b and R_6b are independently H or F; A and B are both isoxazolines; m = 1; R_1a is selected from R_1a3; and R_1b is selected from -N(R_5)-HET-1A and HET-2A, in particular HET-1A as isoxazolyl, 1,2,5-thiadiazolyl or isothiazolyl and HET-2A as 1,2,3-triazol-1-yl (optionally substituted) or tetrazol-2-yl.

In one embodiment is provided a compound of formula (I) or a pharmaceutically-acceptable salt or an in-vivo hydrolysable ester thereof, wherein group C is selected from groups D, E and H; R_2b and R_6b are independently H or F; either A or B is an oxazolidinone and the other is an isoxazoline; m = 1; R_1a is selected from R_1a3; and R_1b is selected from OH, -NHCOMe, -NHCOcyclopropyl, -NH(C=S)OMe and -NHCOOMe.

In one embodiment is provided a compound of formula (I) or a pharmaceutically-acceptable salt or an in-vivo hydrolysable ester thereof, wherein group C is selected from groups D, E and H; R_2b and R_6b are independently H or F; either A or B is an oxazolidinone and the other is an isoxazoline; m = 1; R_1a is selected from R_1a3; and R_1b is selected from -N(R_5)-HET-1A and HET-2A, in particular HET-1A as isoxazolyl, 1,2,5-thiadiazolyl or isothiazolyl and HET-2A as 1,2,3-triazol-1-yl (optionally substituted) or tetrazol-2-yl.

In one embodiment is provided a compound of formula (I) or a pharmaceutically-acceptable salt or an in-vivo hydrolysable ester thereof, wherein group C is selected from groups D, E and H; R_2b and R_6b are independently H or F; A and B are both oxazolidinones; m = 2; and R_1b is selected from OH, -NHCOMe, -NHCOcyclopropyl, -NH(C=S)OMe and -NHCOOMe.

In one embodiment is provided a compound of formula (I) or a pharmaceutically-acceptable salt or an in-vivo hydrolysable ester thereof, wherein group C is selected from groups D, E and H; R_2b and R_6b are independently H or F; A and B are both oxazolidinones; m = 2; and R_1b is selected from -N(R_5)-HET-1A and HET-2A, in particular HET-1A as isoxazolyl, 1,2,5-thiadiazolyl or isothiazolyl and HET-2A as 1,2,3-triazol-1-yl (optionally substituted) or tetrazol-2-yl.

In one embodiment is provided a compound of formula (I) or a pharmaceutically-acceptable salt or an in-vivo hydrolysable ester thereof, wherein group C is selected from groups D, E and H; R_2b and R_6b are independently H or F; A and B are both isoxazolines; m = 2; and R_1b is selected from OH, -NHCOMe, -NHCOcyclopropyl, -NH(C=S)OMe and -NHCOOMe.

In one embodiment is provided a compound of formula (I) or a pharmaceutically-acceptable salt or an in-vivo hydrolysable ester thereof, wherein group C is selected from groups D, E and H; R_2b and R_6b are independently H or F; A and B are both isoxazolines; m = 2; and R_1b is selected from -N(R_5)-HET-1A and HET-2A, in particular HET-1A as isoxazolyl, 1,2,5-thiadiazolyl or isothiazolyl and HET-2A as 1,2,3-triazol-1-yl (optionally substituted) or tetrazol-2-yl.

In one embodiment is provided a compound of formula (I) or a pharmaceutically-acceptable salt or an in-vivo hydrolysable ester thereof, wherein group C is selected from groups D, E and H; R_2b and R_6b are independently H or F; either A or B is an oxazolidinone and the other is an isoxazoline; m = 2; and R_1b is selected from OH, -NHCOMe, -NHCOcyclopropyl, -NH(C=S)OMe and -NHCOOMe.

In one embodiment is provided a compound of formula (I) or a pharmaceutically-acceptable salt or an in-vivo hydrolysable ester thereof, wherein group C is selected from groups D, E and H; R_2b and R_6b are independently H or F; either A or B is an oxazolidinone and the other is an isoxazoline; m = 2; and R_1b is selected from -N(R_5)-HET-1A and HET-2A, in particular HET-1A as isoxazolyl, 1,2,5-thiadiazolyl or isothiazolyl and HET-2A as 1,2,3-triazol-1-yl (optionally substituted) or tetrazol-2-yl.

In all of the above definitions the preferred compounds are as shown in formula (IA).

Particular compounds of the present invention include each individual compound described in the Examples, especially Examples 2, 4 and 5.

Process section:

In a further aspect the present invention provides a process for preparing a compound of invention or a pharmaceutically-acceptable salt or an in-vivo hydrolysable ester thereof. It will be appreciated that during certain of the following processes certain substituents may require protection to prevent their undesired reaction. The skilled chemist will appreciate when such protection is required, and how such protecting groups may be put in place, and later removed.

For examples of protecting groups see one of the many general texts on the subject, for example, 'Protective Groups in Organic Synthesis' by Theodora Green (publisher: John Wiley & Sons). Protecting groups may be removed by any convenient method as described in the literature or known to the skilled chemist as appropriate for the removal of the protecting group in question, such methods being chosen so as to effect removal of the protecting group with minimum disturbance of groups elsewhere in the molecule.

Thus, if reactants include, for example, groups such as amino, carboxy or hydroxy it may be desirable to protect the group in some of the reactions mentioned herein.

A suitable protecting group for an amino or alkylamino group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an alkoxycarbonyl group, for example a methoxycarbonyl, ethoxycarbonyl or *t*-butoxycarbonyl group, an arylmethoxycarbonyl group, for example benzyloxycarbonyl, or an aroyl group, for example benzoyl. The deprotection conditions for the above protecting groups necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or alkoxycarbonyl group or an aroyl group may be removed for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an acyl group such as a *t*-butoxycarbonyl group may be removed, for example, by treatment with a suitable acid as hydrochloric, sulfuric or phosphoric acid or trifluoroacetic acid and an arylmethoxycarbonyl group such as a benzyloxycarbonyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon, or by treatment with a Lewis acid for example boron tris(trifluoroacetate). A suitable alternative protecting group

for a primary amino group is, for example, a phthaloyl group which may be removed by treatment with an alkylamine, for example dimethylaminopropylamine, or with hydrazine.

A suitable protecting group for a hydroxy group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an aroyl group, for example benzoyl, or an arylmethyl group, for example benzyl. The deprotection conditions for the above protecting groups will necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or an aroyl group may be removed, for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an arylmethyl group such as a benzyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

A suitable protecting group for a carboxy group is, for example, an esterifying group, for example a methyl or an ethyl group which may be removed, for example, by hydrolysis with a base such as sodium hydroxide, or for example a *t*-butyl group which may be removed, for example, by treatment with an acid, for example an organic acid such as trifluoroacetic acid, or for example a benzyl group which may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon. Resins may also be used as a protecting group.

The protecting groups may be removed at any convenient stage in the synthesis using conventional techniques well known in the chemical art.

A compound of the invention, or a pharmaceutically-acceptable salt or an *in vivo* hydrolysable ester thereof, may be prepared by any process known to be applicable to the preparation of chemically-related compounds. Such processes, when used to prepare a compound of the invention, or a pharmaceutically-acceptable salt or an *in vivo* hydrolysable ester thereof, are provided as a further feature of the invention and are illustrated by the following representative examples. Necessary starting materials may be obtained by standard procedures of organic chemistry (see, for example, Advanced Organic Chemistry (Wiley-Interscience), Jerry March or Houben-Weyl, Methoden der Organischen Chemie). The preparation of such starting materials is described within the accompanying non-limiting Examples. Alternatively, necessary starting materials are obtainable by analogous procedures to those illustrated which are within the ordinary skill of an organic chemist. Information on the preparation of necessary starting materials or related compounds (which may be adapted to form necessary starting materials) may also be found in the certain Patent Application Publications, the contents of the relevant process sections of which are hereby incorporated herein by reference; for example WO 94-13649; WO 98-54161; WO 99-64416;

WO 99-64417; WO 00-21960; WO 01-40222.

The skilled organic chemist will be able to use and adapt the information contained and referenced within the above references, and accompanying Examples therein and also the Examples herein, to obtain necessary starting materials, and products. For example, the skilled chemist will be able to apply the teaching herein for compounds of formula (I) in which two central phenyl groups are present (that is when group C is group D) to prepare compounds in which group C is any of groups E to O as hereinbefore defined. Similarly, in the processes illustrated below the skilled chemist will be able to apply the teaching as necessary to prepare compounds in which for instance both rings A and B are isoxazoline and those compounds in which one of rings A and B is isoxazoline and the other oxazolidinone.

Thus, the present invention also provides that the compounds of the invention and pharmaceutically-acceptable salts and *in vivo* hydrolysable esters thereof, can be prepared by a process (a) to (h) as follows (wherein the variables are as defined above unless otherwise stated):

a) by modifying a substituent in, or introducing a substituent into another compound of the invention by using standard chemistry (see for example, Comprehensive Organic Functional Group Transformations (Pergamon), Katritzky, Meth-Cohn & Rees or Advanced Organic Chemistry (Wiley-Interscience), Jerry March or Houben-Weyl, Methoden der Organischen Chemie)); for example:

an acylamino group may be converted into a thioacylamino group;

an acylamino group or thioacylamino group may be converted into another acylamino or thioacylamino; heterocyclyl for instance tetrazolyl or thiazolyl, or heterocyclylamino group (optionally substituted or protected on the amino-nitrogen atom), a heterocyclyl group linked through nitrogen (optionally substituted on a carbon other than a carbon adjacent to the linking nitrogen atom), for instance an optionally 4-substituted 1,2,3-triazol-1-yl group; or an amidino group; such conversions of the acylamino group taking place either directly or through through the intermediacy of one or more derivatives such as an amino group;

an acyloxy group may be converted into a hydroxy group or into the groups that may be obtained from a hydroxy group (either directly or through the intermediacy of a hydroxy group);

an alkyl halide such as alkylbromide or alkyliodide may be converted into an alkyl fluoride or nitrile;

an alkyl sulfonate such as alkyl methanesulfonate may be converted into an alkyl fluoride or nitrile;

an alkylthio group such as methylthio may be converted into a methanesulfinyl ormethanesulfonyl group;

an arylthio group such as phentlthio may be converted into a benzenesulfinyl or benzenesulfonyl group;

an amidino or guanidino group may be converted into a range of 2-substituted 1,3-diazoles and 1,3-diazines;

an amino group may be converted for instance into acylamino or thioacylamino for instance an acetamide (optionally substituted), alkyl- or dialkyl-amino and thence into a further range of N-alkyl-amine derivatives, sulfonylamino, sulfinylamino, amidino, guanidino, arylamino, heteroarylamino, N-linked heterocyclic for instance an optionally 4-substituted 1,2,3-triazol-1-yl group;

an aryl- or heteroary-halide group such as an aryl- or hetero-aryl chloride or bromide or iodide may be converted by transition metal mediated coupling, especially Pd(0) mediated coupling into a range of aryl-, heteroaryl, alkenyl, alkynyl, acyl, alkylthio, or alkyl- or dialkyl-amino substituted aryl or heteroaryl groups;

an aryl- or heteroary-sulfonate group such as an aryl- or hetero-aryl trifluoromethanesulfonate may be converted by transition metal mediated coupling, especially Pd(0) mediated coupling into a range of aryl-, heteroaryl, alkenyl, alkynyl, acyl, alkylthio, or alkyl- or dialkyl-amino substituted aryl or heteroaryl groups;

an aryl- or heteroary-halide group such as an aryl- or hetero-aryl chloride or bromide or iodide may be converted by transition metal mediated coupling, especially Pd(0) mediated coupling into a range of trialkyltin, dialkylboronate, trialkoxysilyl, substituted aryl or heteroaryl groups useful as intermediates for the synthesis of compounds of the invention;

an azido group may be converted for instance into a 1,2,3-triazolyl or amine and thence by methods that are well known in the art into any of the range common amine derivatives.such as acylamino for instance acetamido group;

a carboxylic acid group may be converted into trifloromethyl, hydroxymethyl, alkoxycarbonyl, aminocarbonyl optionally substituted on nitrogen, formyl, or acyl groups;

a cyano group may be converted into a tetrazole, or an imidate, an amidine, an amidrazone, an N-hydroxyamidrazone, an amide, a thioamide, an ester, or an acid and thence by methods that

are well known in the art into any of the range of heterocycles derived from such nitrile derivatives;

a hydroxy group may be converted for instance into an alkoxy, cyano, azido, alkylthio, keto and oximino, fluoro, bromo, chloro, iodo, alkyl- or aryl-sulfonyloxy for instance trifluoromethanesulfonate, methanesulfonate, or tosylsulfonate, silyloxy ; acylamino or thioacylamino , for instance an acetamide (optionally substituted or protected on the amido-nitrogen atom); acyloxy, for instance an acetoxy; phosphono-oxy, heterocyclylamino (optionally substituted or protected on the amino-nitrogen atom), for instance an isoxazol-3-ylamino or a 1,2,5-thiadiazol-3-ylamino; heterocyclyl linked through nitrogen (optionally substituted on a carbon other than a carbon atom adjacent to the linking nitrogen ring atom), for instance an optionally 4-substituted 1,2,3-triazol-1-yl; or amidino, for instance an 1-(N-cyanoimino)ethylamino group; such conversions of the hydroxy group taking place directly (for instance by acylation or Mitsunobu reaction) or through the intermediacy of one or more derivatives (for instance a mesylate or an azide);

a silyloxy group may be converted into a hydroxy group or into the groups that may be obtained from a hydroxy group (either directly or through the intermediacy of a hydroxy group);

a keto group may be converted into a hydroxy, thiocarbonyl, oximino, or difluoro group;

a nitro-group may be converted into an amino group and thence by methods that are well known in the art into any of the range common amine derivatives.such as acylamino for instance acetamido group;

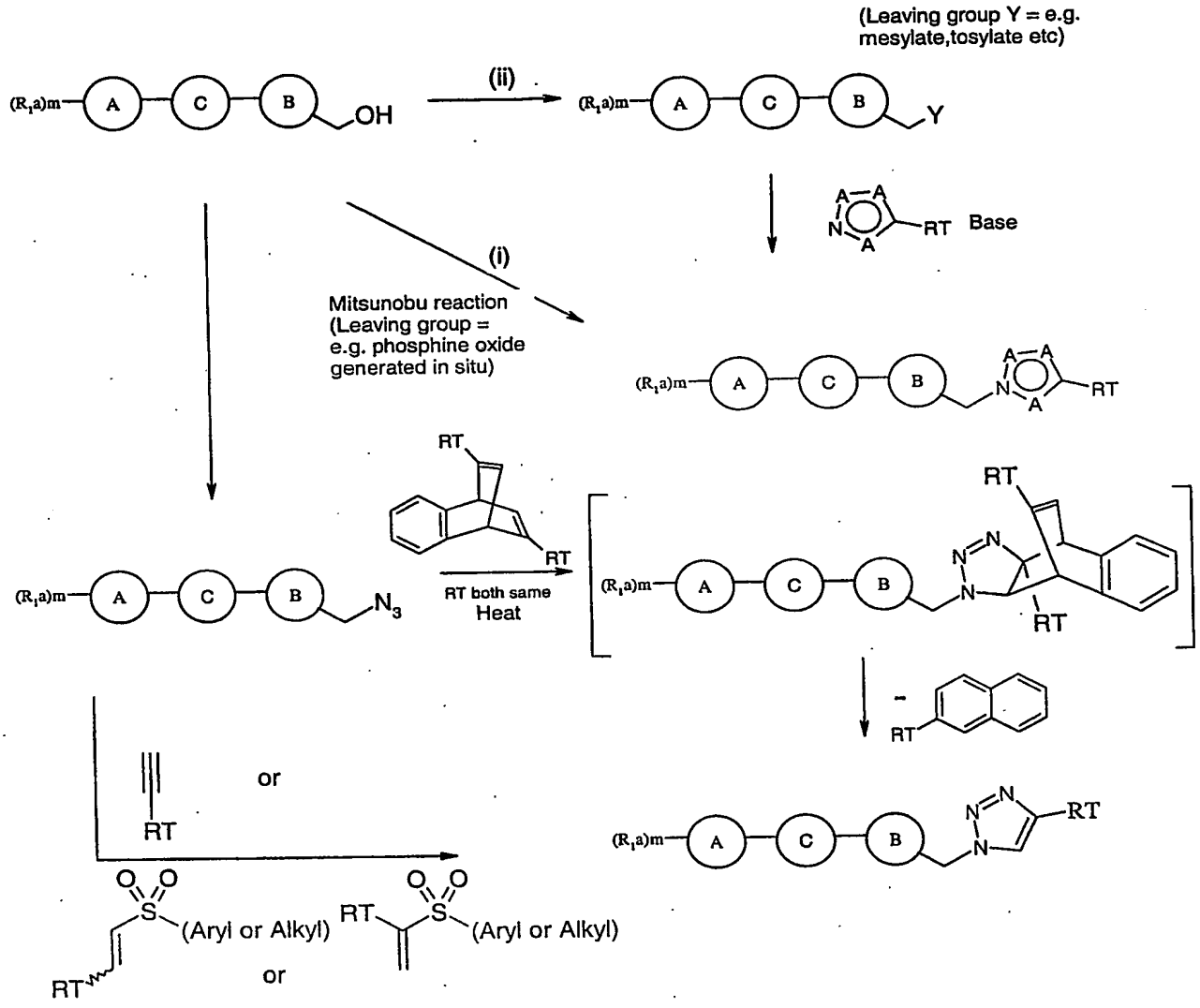
an optionally substituted aromatic or heteroaromatic ring C'may be converted into another aromatic or heteroaromatic ring C' by introduction of a new substituent (R2a to R6a or R2a' or R6a') or by refunctionalisation of an existing substituent (R2a to R6a or R2a' or R6a');

a heterocyclylamino group (optionally substituted or protected on the amino-nitrogen atom) may be converted into another heterocyclyl amino group (optionally substituted or protected on the amino-nitrogen atom) by refunctionalisation, for instance by protection or deprotection, of the amino-nitrogen atom, by introduction of a new ring substituent, or by refunctionalisation of an existing ring substituent;

a heterocyclyl group linked through nitrogen (optionally substituted on a carbon other than a carbon atom adjacent to the linking nitrogen ring atom) may be converted into another heterocyclyl group linked through nitrogen (optionally substituted on a carbon other than a carbon atom adjacent to the linking nitrogen ring atom) by introduction of a new ring

substituent or by refunctionalisation of an existing ring substituent, for instance by modifying the 4-substituent of a 4-substituted 1,2,3-triazol-1-yl group.

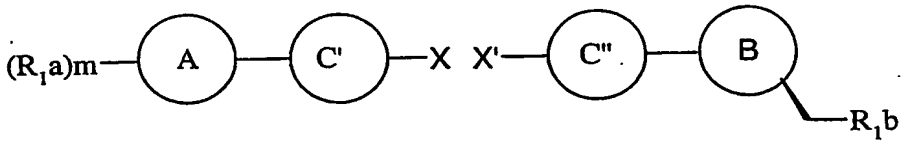
For instance, examples drawn from the methods for conversion of a hydroxy group into an optionally substituted triazole group are illustrated by the scheme:



Examples drawn from the range of regioselective methods that proceed under very mild conditions are further illustrated by processes (f), (g), and (h).

b) by reaction of a molecule of a compound of formula (IIa) (wherein X is a leaving group useful in palladium coupling, for example boronate, trimethyl tin, iodo and bromo) with a molecules of a compound of formula (IIb) (wherein X' is a leaving group useful in palladium coupling, for example boronate, trimethyl tin, iodo and bromo) wherein X and X' are chosen such that an aryl-aryl, heteroaryl-aryl, or heteroaryl-heteroaryl bond replaces the

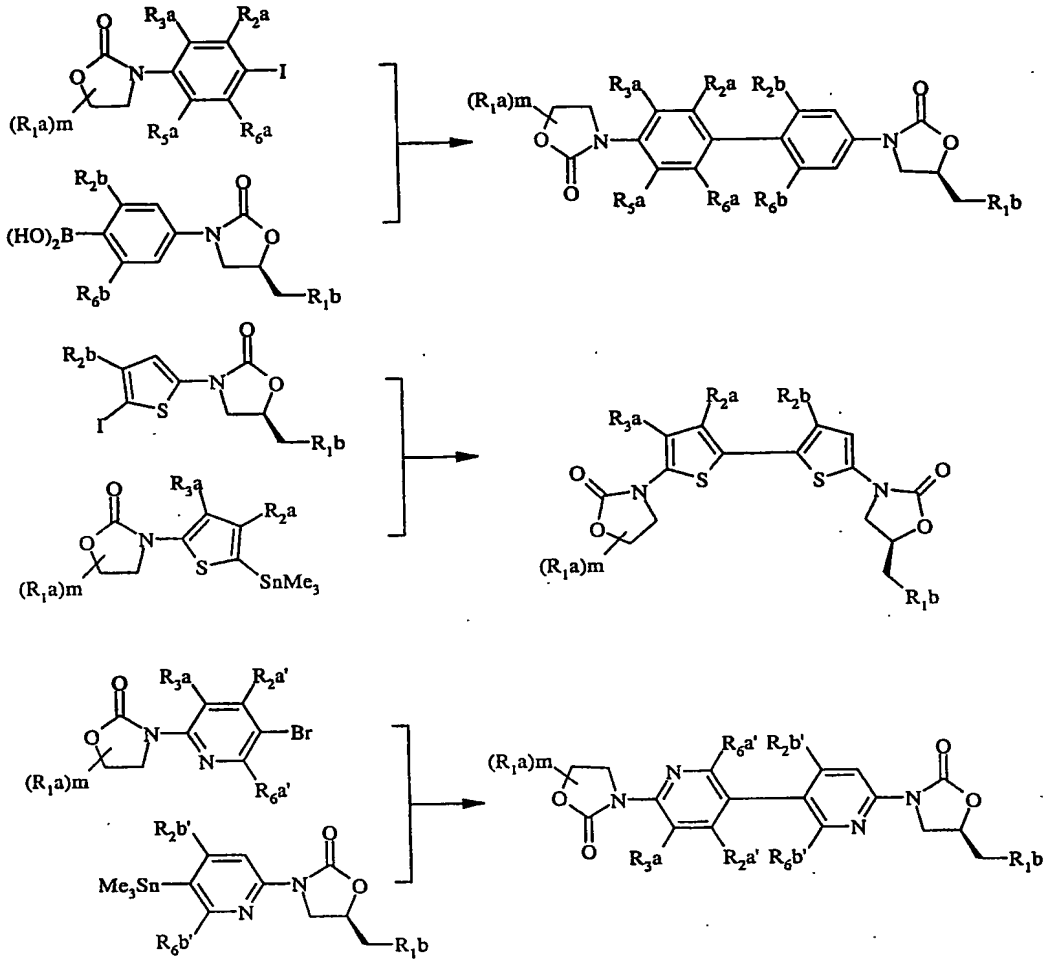
aryl-X (or heteroaryl-X) and aryl-X' (or heteroaryl-X') bonds. Such methods are now well known, see for instance see for instance J.K. Stille, *Angew Chem. Int. Ed. Eng.*, **1986**, *25*, 509-524; N. Miyaura and A Suzuki, *Chem. Rev.*, **1995**, *95*, 2457-2483, D. Baranano, G. Mann, and J.F. Hartwig, *Current Org. Chem.*, **1997**, *1*, 287-305, S.P. Stanforth, *Tetrahedron*, 54 **1998**, 263-303, and P.R. Parry, C. Wang, A.S. Batsanov, M.R. Bryce, and B. Tarbit, *J. Org. Chem.*, **2002**, *67*, 7541-7543.

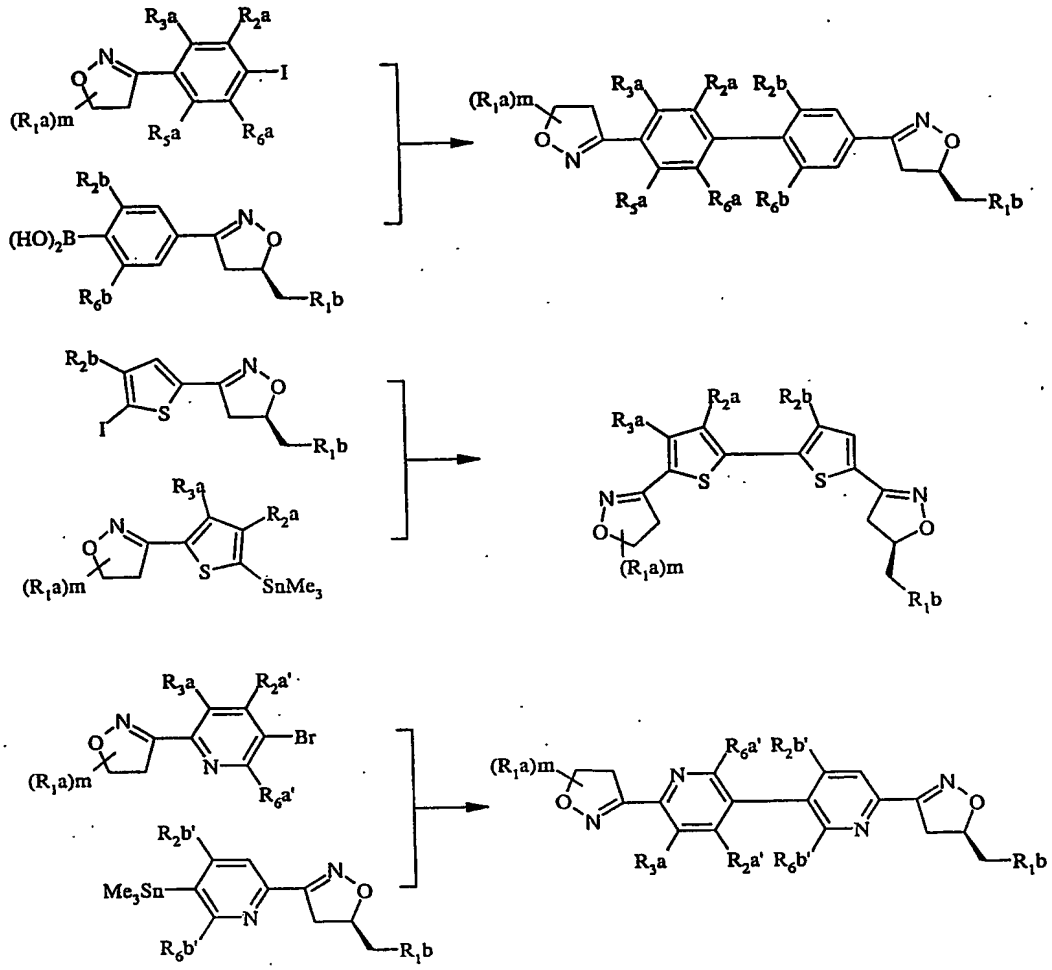


(IIa) **(IIb)**

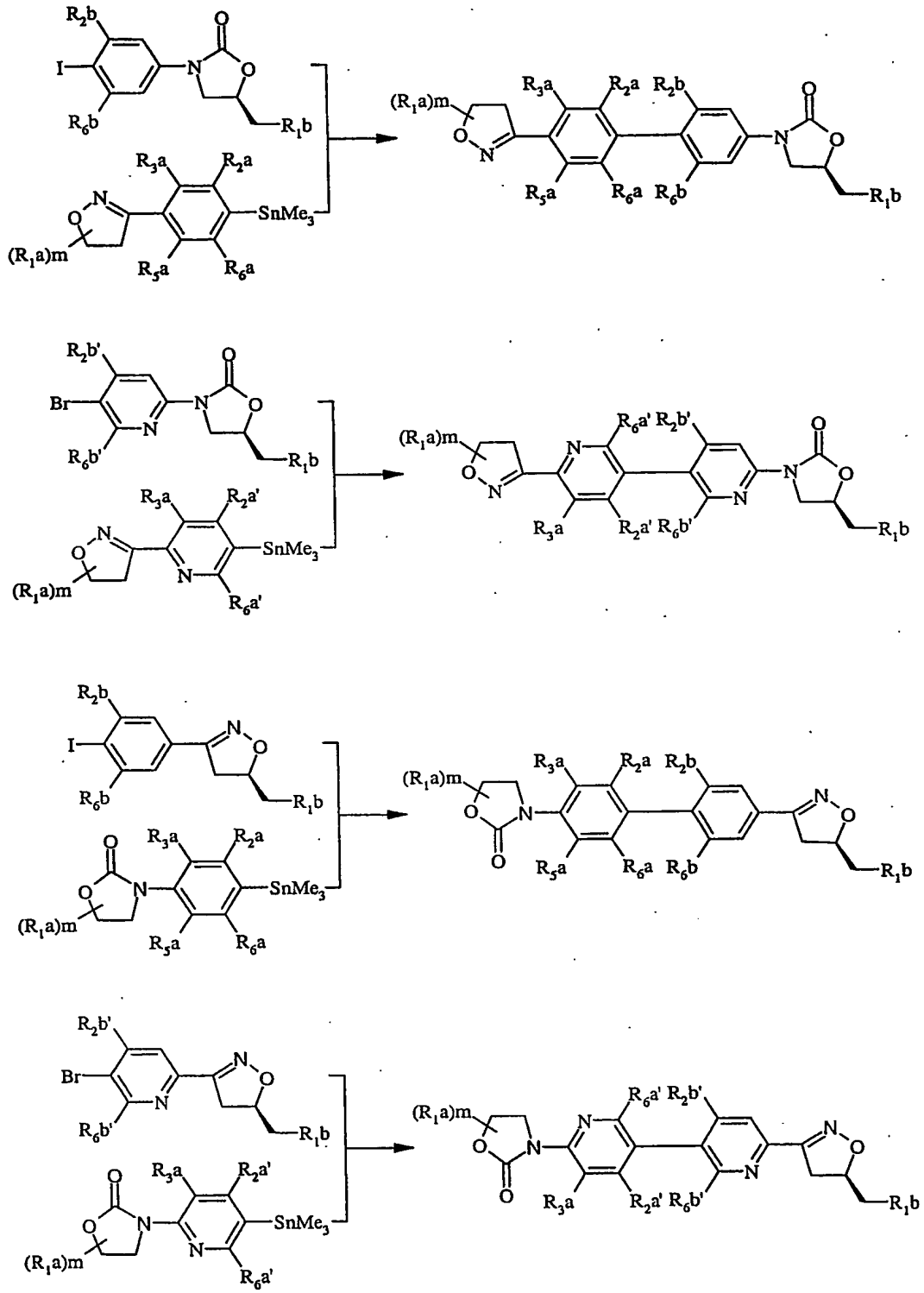
The leaving groups X and X' may be chosen to be the same and lead to symmetrical molecules of formula (I) or different and chosen to lead to symmetrical or unsymmetrical molecules of formula (I).

For example





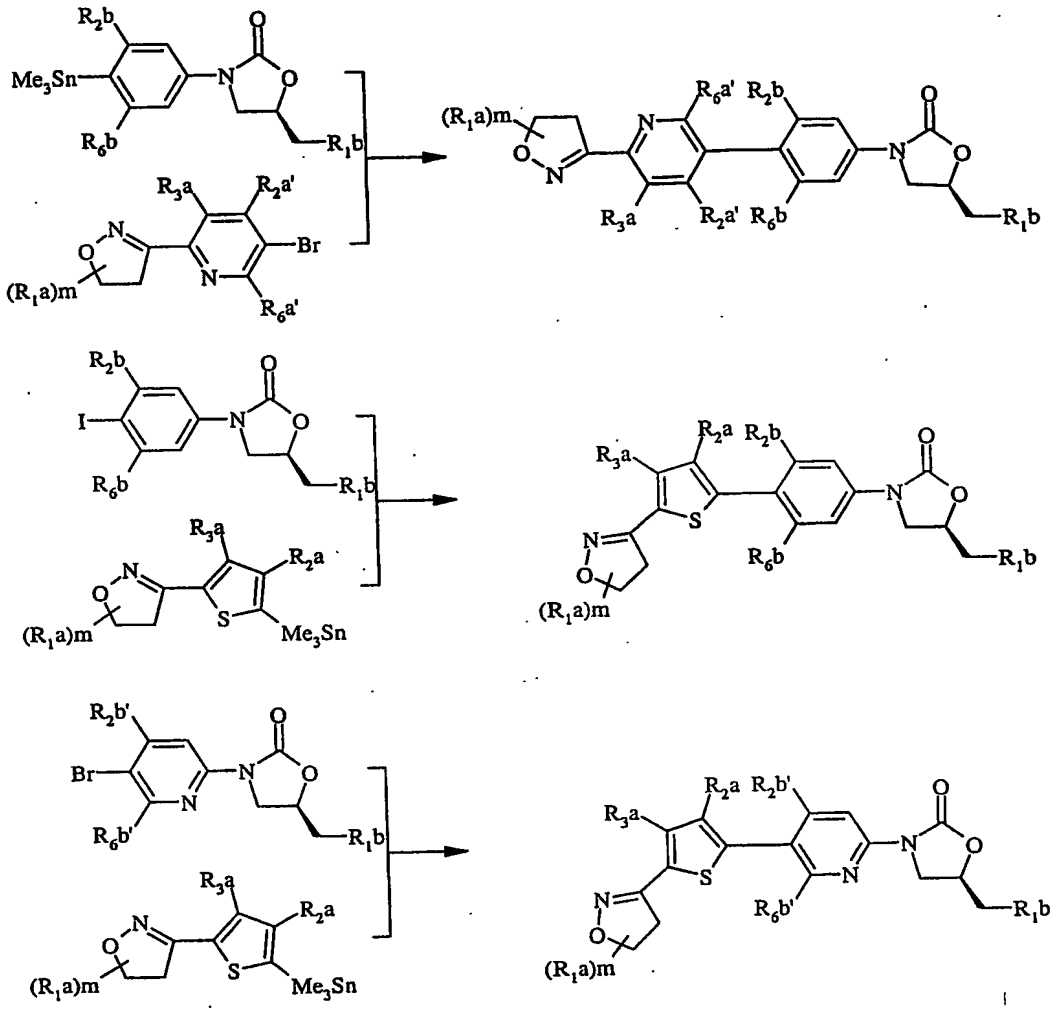
Similarly, this chemistry may be applied to two dissimilar molecules of formula (II), for example those in which ring A is not the same as ring B, wherein X is suitably selected to enable unsymmetrical coupling so that an aryl-aryl, heteroaryl-aryl, or heteroaryl-heteroaryl bond replaces the aryl-X (or heteroaryl-X) and the aryl-X' (or heteroaryl-X') bonds. For example



Furthermore, this chemistry may also be applied to two dissimilar molecules of formula (II), for example those in which ring C' is not the same as ring C'', wherein X and X' are suitably selected to enable unsymmetrical coupling so that an aryl-aryl, heteroaryl-aryl, or heteroaryl-

heteroaryl bond replaces the two different aryl-X (or heteroaryl-X) and the aryl-X' (or heteroaryl-X') bonds.

For example



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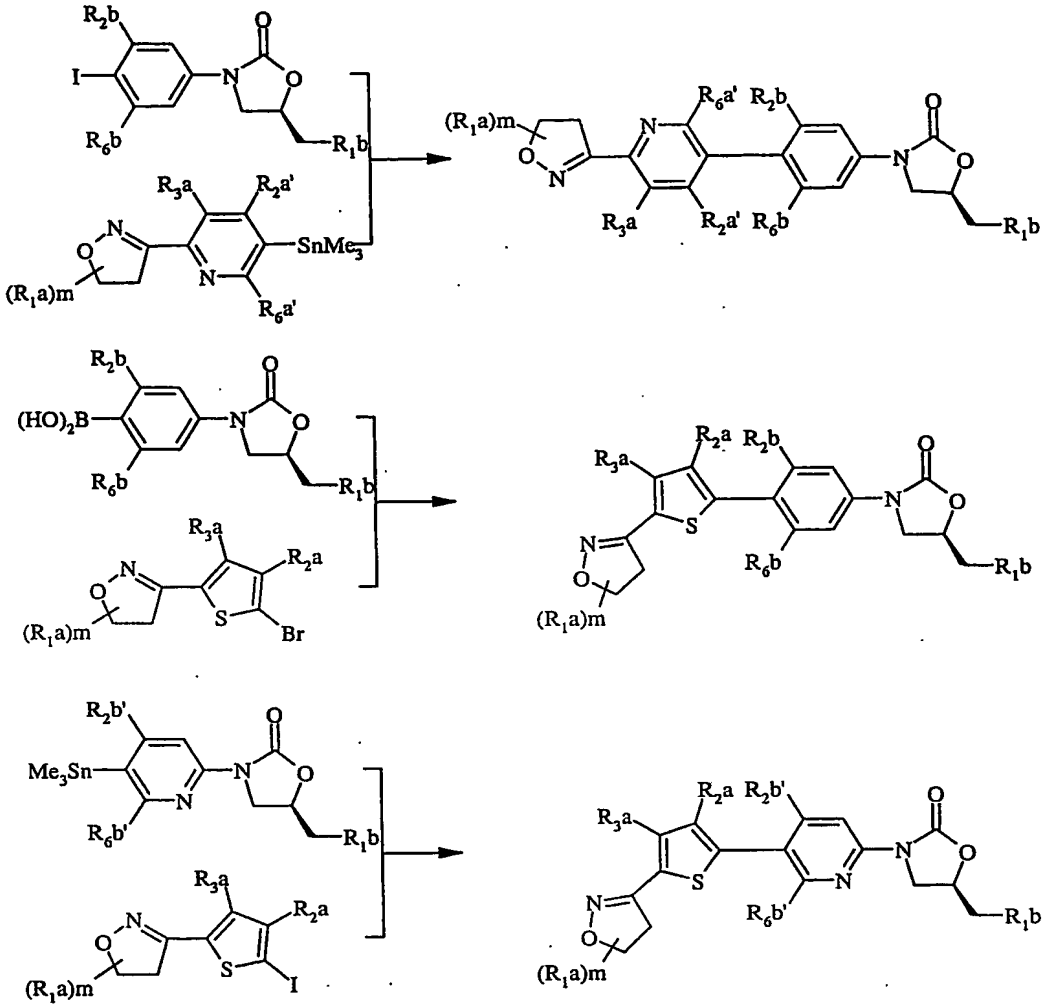
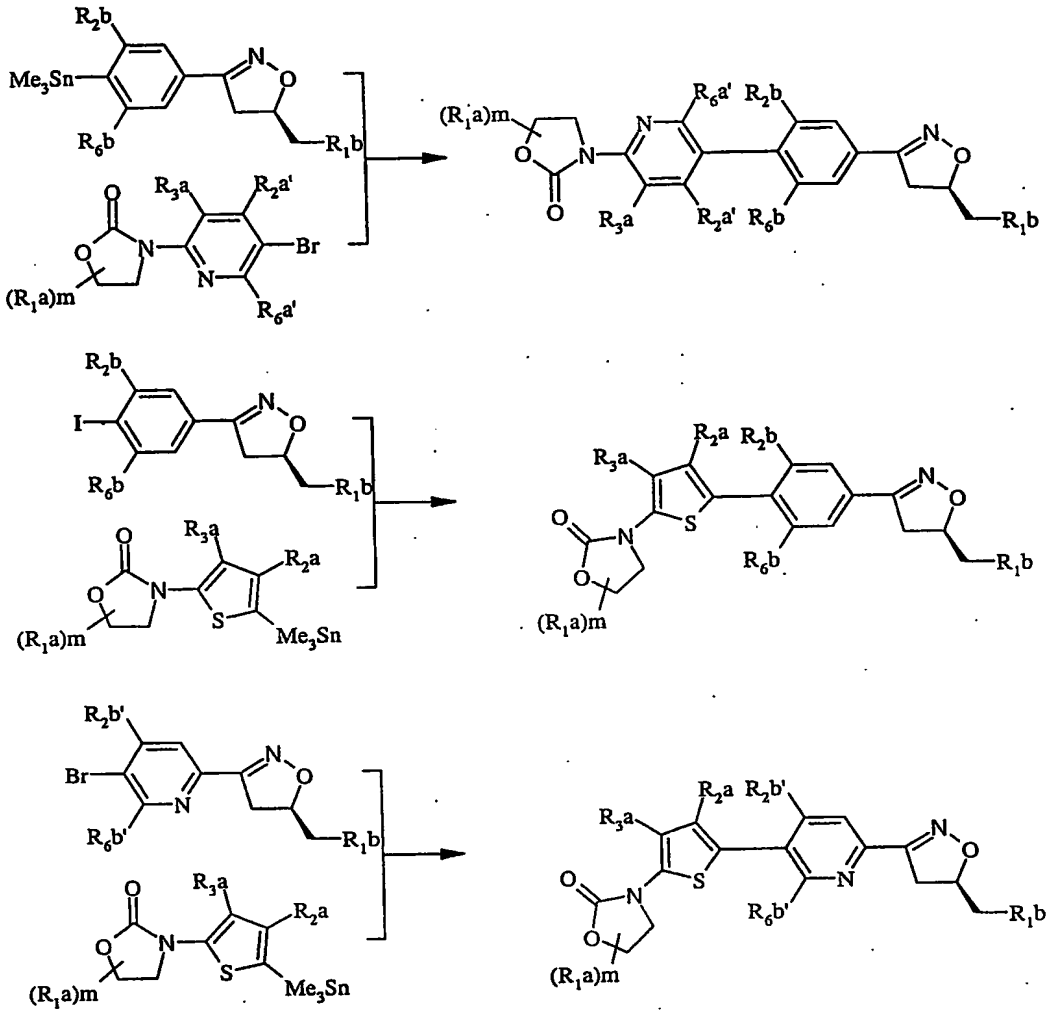
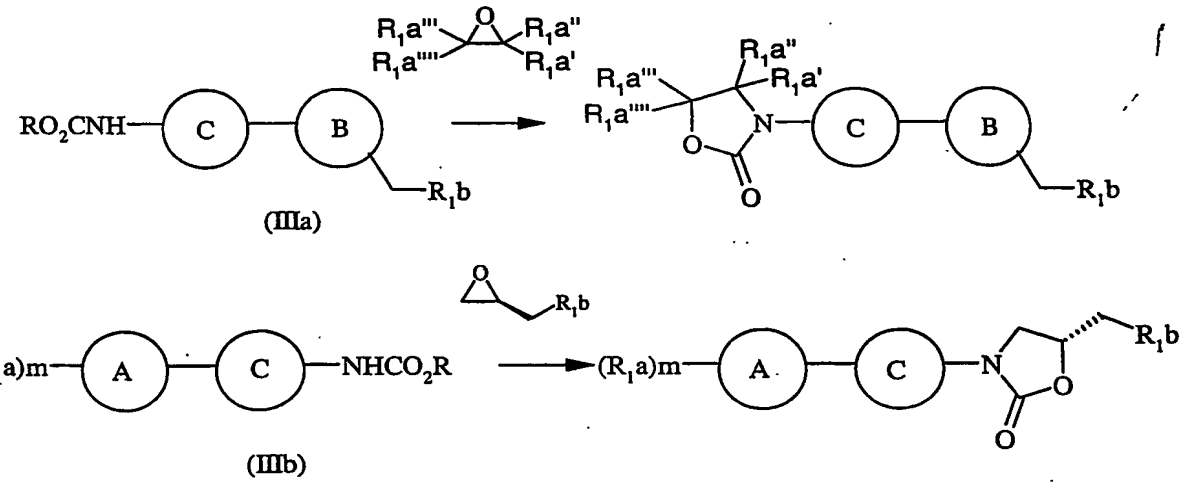




The aryl isoxazolines and aryl oxazolidinones required as reagents for process b) or as intermediates for the preparation of reagents for process b) may be prepared by standard organic methods, for instance by methods analogous to those set out in process sections c) and h). Methods for the introduction and interconversion of Groups X and X' are well known in the art.

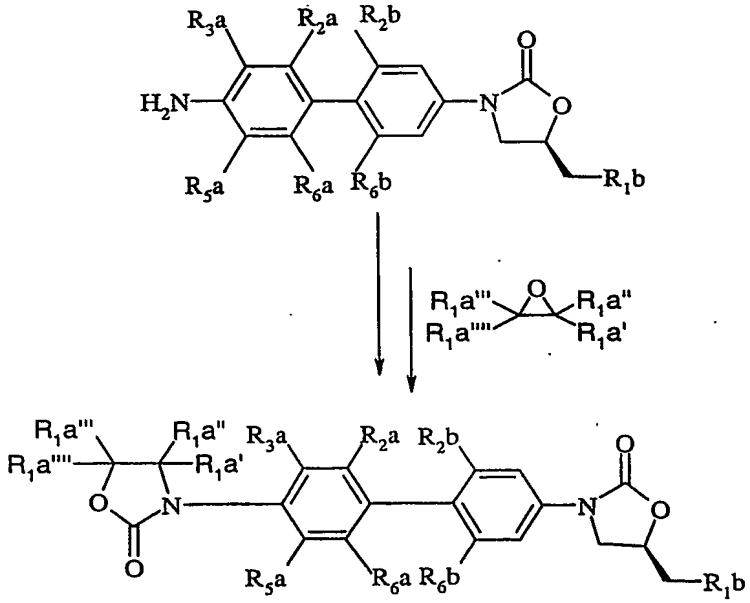
c) by reaction of a (hetero)biaryl derivative (IIIa) or (IIIb) carbamate with an appropriately substituted oxirane (wherein 0, 1, or 2 of R_1a'-R_1a'''' are substitutents as defined for R_1a and the remainder are hydrogen) to form an oxazolidinone ring at the undeveloped aryl position.



(IIIa)

(IIIb)

Variations on this process in which the carbamate is replaced by an isocyanate or by an amine or/and in which the oxirane is replaced by an equivalent reagent X-$C(R_1a')(R_1a'')C(R_1a''')$(O-optionally protected)$(R_1a'''')$ or X-CH_2CH(O-optionally protected)CH_2R_1b where X is a displaceable group are also well known in the art. For example,



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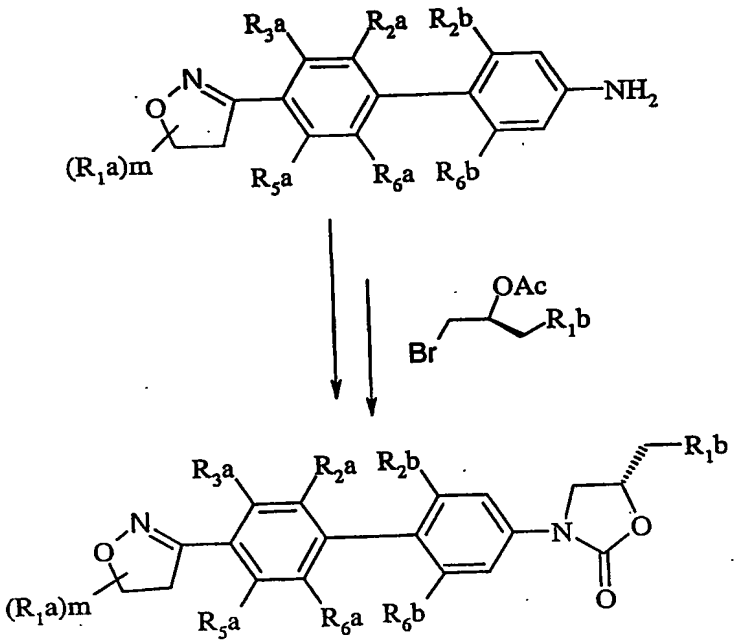
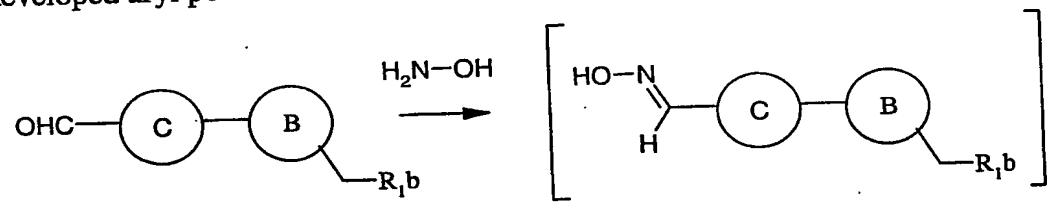
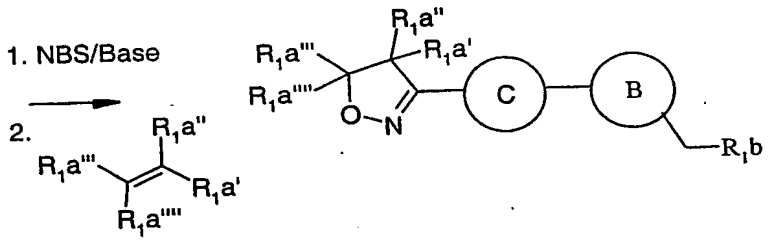
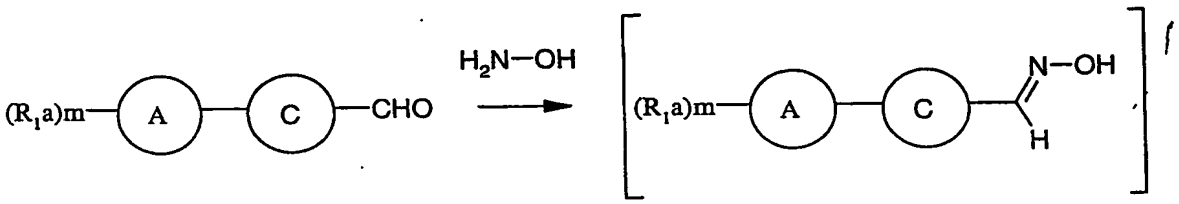


d) by reaction of a (hetero)biaryl derivative (IVa) or (IVb) to form an isoxazoline ring at the undeveloped aryl position.

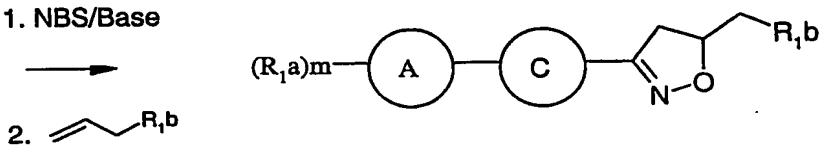


(IVa) (IVa')

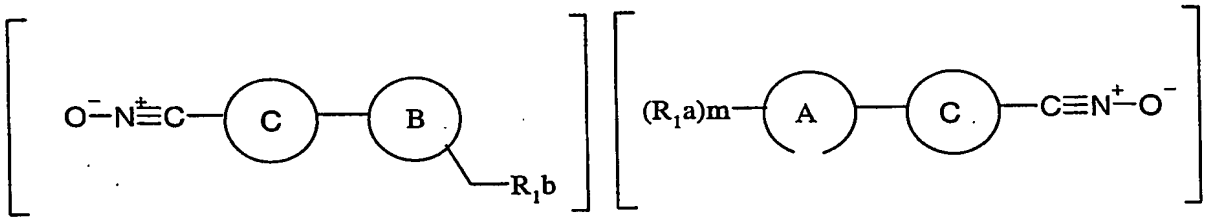




(IVb) (IVb')

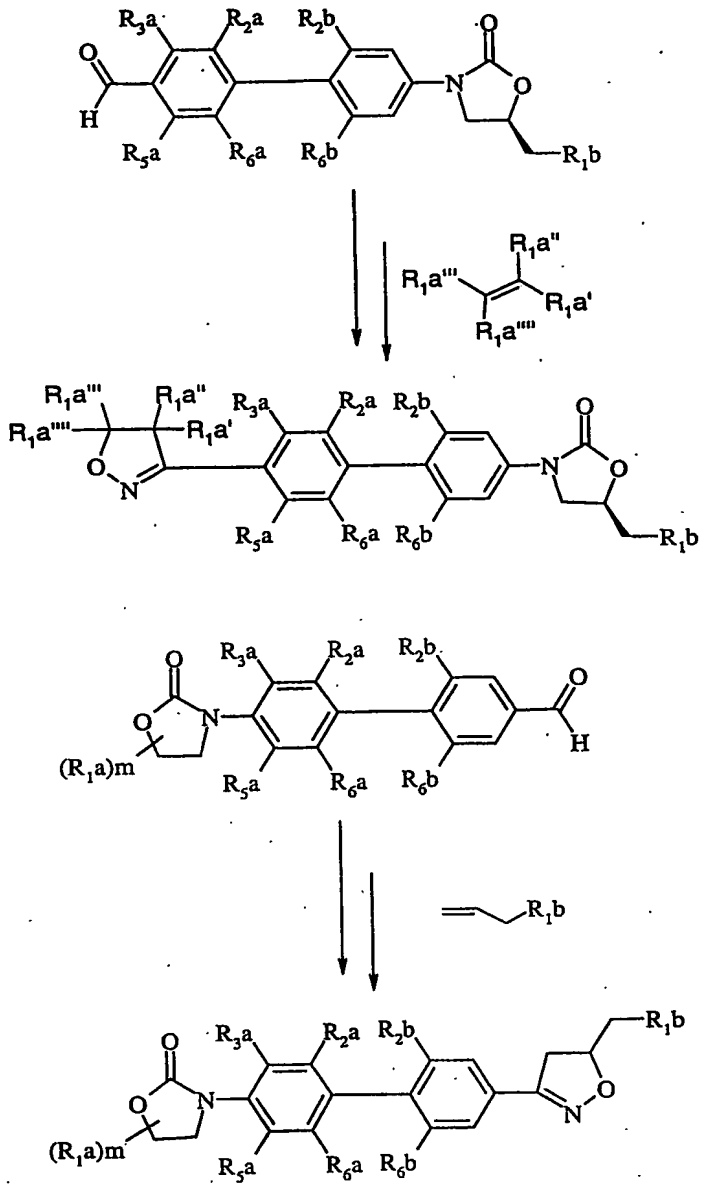


Variations on this process in which the reactive intermediate (a nitrile oxide IVa'' or IVb'') is obtained other than by oxidation of an oxime (IVa') or (IVb') are well known in the art.

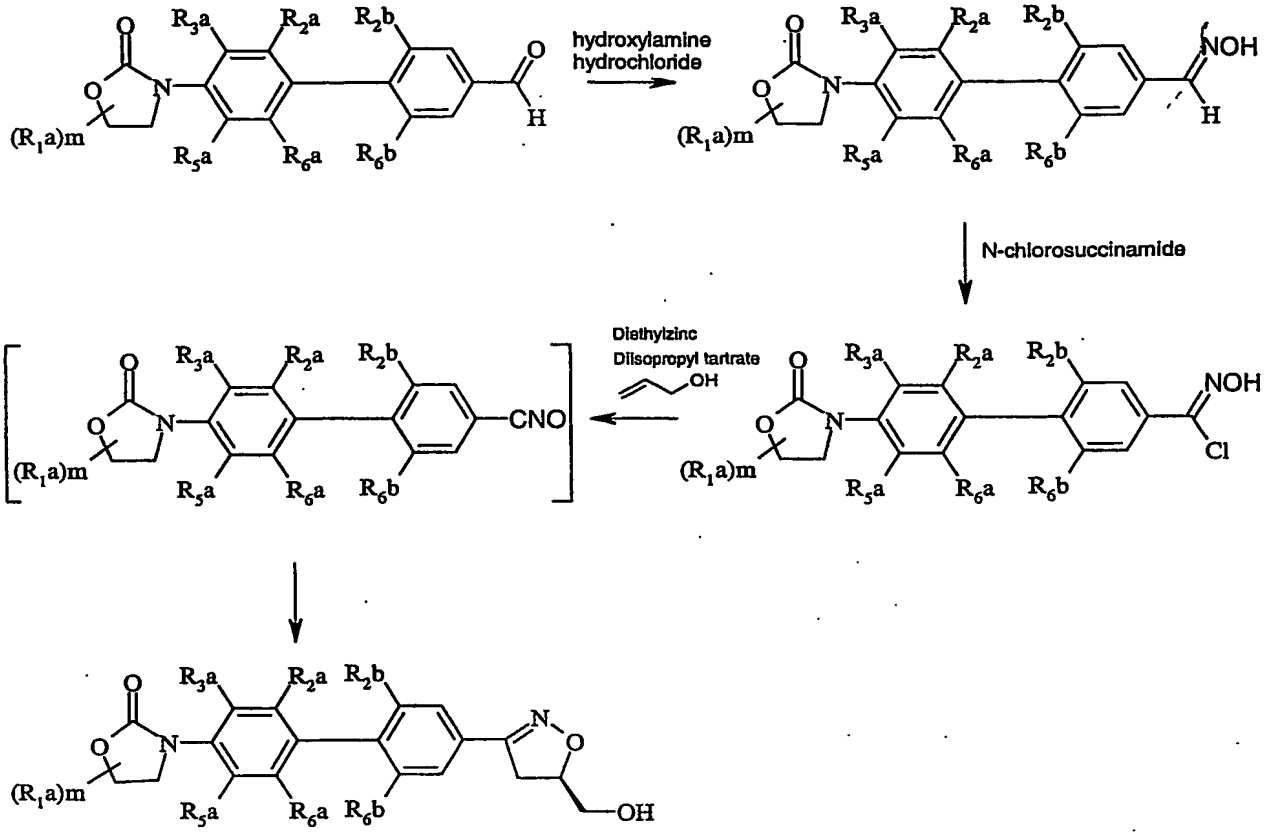


(IVa'') (IVb'')

For example, oxidation of an appropriately substituted biphenylcarboxaldehyde oxime in the presence of an appropriately substituted allyl derivative gives an isoxazoline of the required structure.

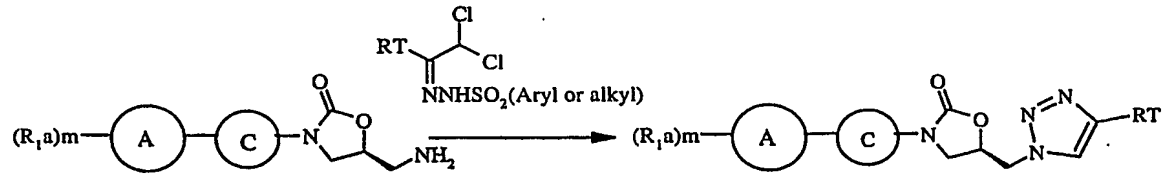


Enantioselective synthesis of 2-isoxazolines via asymmetric cycloaddition of nitrile oxides to olefins has been achieved by the use of chiral auxiliaries. For instance, when the alcohol is an allyl alcohol the desired stereochemistry at ring B can be obtained in reactions conducted in the presence of (*R,R*)-diisopropyl tartrate (or (*S,S*)-diisopropyl tartrate depending on the desired stereochemistry) as a chiral auxiliary (Yutaka Ukaji *et al. Chem. Letters*, **1993**, 1847-1850). Other chiral auxiliaries may also be employed with other olefins (see for instance Takahiko Akayama et al., Tet. Letters, 1992, 33, 5763-5766; and Jeffrey Stack et al., Tetrahedron, 1993, 49, 995-1008 and references therein).



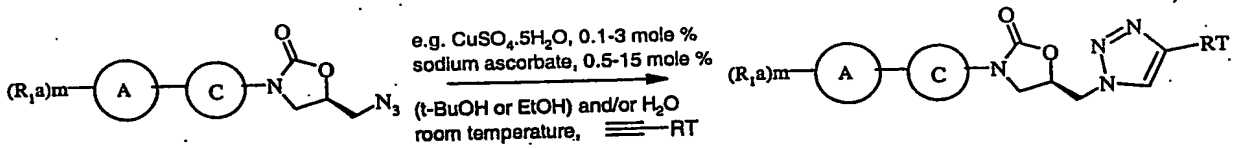
(e) for HET as optionally substituted 1,2,3-triazoles, compounds of the formula (I) may be made by cycloaddition via the azide (wherein e.g. Y in (II) is azide) to acetylenes, or to acetylene equivalents such as optionally substituted cylcohexa-1,4-dienes or optionally substituted ethylenes bearing eliminatable substituents such as arylsulfonyl;

(f) for HET as 4-substituted 1,2,3-triazole compounds of formula (I) may be made by reacting aminomethyloxazolidinones with 1,1-dihaloketone sulfonylhydrazones (Sakai, Kunihazu; Hida, Nobuko; Kondo, Kiyosi; *Bull. Chem. Soc. Jpn.*, **59**, *1986*, 179-183; Sakai, Kunikazu; Tsunemoto, Daiei; Kobori, Takeo; Kondo, Kiyoshi; Hido, Noboko EP 103840 A2 19840328); for instance

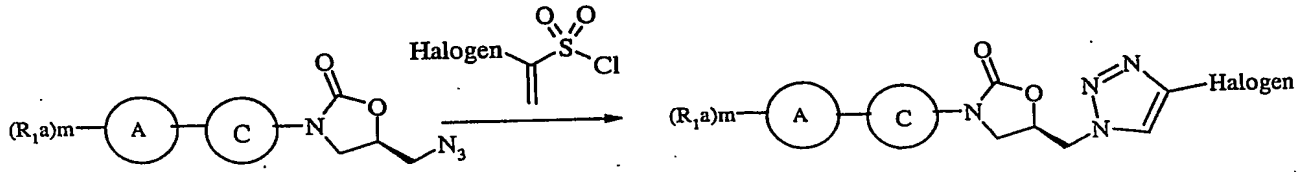


(g) for HET as 4-substituted 1,2,3-triazole compounds of formula (I) may also be made by reacting azidomethyl oxazolidinones with terminal alkynes using Cu(I) catalysis in e.g. aqueous alcoholic solution at ambient temperatures to give 4-substituted 1,2,3-triazoles (V.V.

Rostovtsev, L.G. Green, V.V. Fokin, and K.B. Sharpless, *Angew. Chem. Int. Ed.*, **2002**, *41*, 2596-2599); for instance



(h) for HET as 4-halogenated 1,2,3-triazole compounds of formula (I) may also be made by reacting azidomethyl oxazolidinones with halovinylsulfonyl chlorides at a temperature between 0 °C and 100 °C either neat or in an inert diluent such as chlorobenzene, chloroform or dioxan; for instance



The removal of any protecting groups, the formation of a pharmaceutically-acceptable salt and/or the formation of an in-vivo hydrolysable ester are within the skill of an ordinary organic chemist using standard techniques. Furthermore, details on the these steps, for example the preparation of in-vivo hydrolysable ester prodrugs has been provided, for example, in the section above on such esters.

When an optically active form of a compound of the invention is required, it may be obtained by carrying out one of the above procedures using an optically active starting material (formed, for example, by asymmetric induction of a suitable reaction step), or by resolution of a racemic form of the compound or intermediate using a standard procedure, or by chromatographic separation of diastereoisomers (when produced). Enzymatic techniques may also be useful for the preparation of optically active compounds and/or intermediates.

Similarly, when a pure regioisomer of a compound of the invention is required, it may be obtained by carrying out one of the above procedures using a pure regioisomer as a starting material, or by resolution of a mixture of the regioisomers or intermediates using a standard procedure.

According to a further feature of the invention there is provided a compound of the invention, or a pharmaceutically-acceptable salt, or in-vivo hydrolysable ester thereof for use in a method of treatment of the human or animal body by therapy.

According to a further feature of the present invention there is provided a method for producing an antibacterial effect in a warm blooded animal, such as man, in need of such

treatment, which comprises administering to said animal an effective amount of a compound of the present invention, or a pharmaceutically-acceptable salt, or in-vivo hydrolysable ester thereof.

The invention also provides a compound of the invention, or a pharmaceutically-acceptable salt, or in-vivo hydrolysable ester thereof, for use as a medicament; and the use of a compound of the invention of the present invention, or a pharmaceutically-acceptable salt, or in-vivo hydrolysable ester thereof, in the manufacture of a medicament for use in the production of an antibacterial effect in a warm blooded animal, such as man.

In order to use a compound of the invention, an in-vivo hydrolysable ester or a pharmaceutically-acceptable salt thereof, including a pharmaceutically-acceptable salt of an in-vivo hydrolysable ester, (hereinafter in this section relating to pharmaceutical composition "a compound of this invention") for the therapeutic (including prophylactic) treatment of mammals including humans, in particular in treating infection, it is normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition.

Therefore in another aspect the present invention provides a pharmaceutical composition which comprises a compound of the invention, an in-vivo hydrolysable ester or a pharmaceutically-acceptable salt thereof, including a pharmaceutically-acceptable salt of an in-vivo hydrolysable ester, and a pharmaceutically-acceptable diluent or carrier.

The pharmaceutical compositions of this invention may be administered in standard manner for the disease condition that it is desired to treat, for example by oral, rectal or parenteral administration. For these purposes the compounds of this invention may be formulated by means known in the art into the form of, for example, tablets, capsules, aqueous or oily solutions or suspensions, (lipid) emulsions, dispersible powders, suppositories, ointments, creams, aerosols (or sprays), drops and sterile injectable aqueous or oily solutions or suspensions.

In addition to the compounds of the present invention the pharmaceutical composition of this invention may also contain or be co-administered (simultaneously, sequentially or separately) with one or more known drugs selected from other clinically useful antibacterial agents (for example, ß-lactams or aminoglycosides) and/or other anti-infective agents (for example, an antifungal triazole or amphotericin). These may include carbapenems, for example meropenem or imipenem, to broaden the therapeutic effectiveness. Compounds of this invention may also contain or be co-administered with bactericidal/permeability-

increasing protein (BPI) products or efflux pump inhibitors to improve activity against gram negative bacteria and bacteria resistant to antimicrobial agents.

A suitable pharmaceutical composition of this invention is one suitable for oral administration in unit dosage form, for example a tablet or capsule which contains between 1mg and 1g of a compound of this invention, preferably between 100mg and 1g of a compound. Especially preferred is a tablet or capsule which contains between 50mg and 800mg of a compound of this invention, particularly in the range 100mg to 500mg.

In another aspect a pharmaceutical composition of the invention is one suitable for intravenous, subcutaneous or intramuscular injection, for example an injection which contains between 0.1% w/v and 50% w/v (between 1mg/ml and 500mg/ml) of a compound of this invention.

Each patient may receive, for example, a daily intravenous, subcutaneous or intramuscular dose of 0.5 $mgkg^{-1}$ to 20 $mgkg^{-1}$ of a compound of this invention, the composition being administered 1 to 4 times per day. In another embodiment a daily dose of 5 $mgkg^{-1}$ to 20 $mgkg^{-1}$ of a compound of this invention is administered. The intravenous, subcutaneous and intramuscular dose may be given by means of a bolus injection. Alternatively the intravenous dose may be given by continuous infusion over a period of time. Alternatively each patient may receive a daily oral dose which may be approximately equivalent to the daily parenteral dose, the composition being administered 1 to 4 times per day.

A pharmaceutical composition to be dosed intravenously may contain advantageously (for example to enhance stability) a suitable bactericide, antioxidant or reducing agent, or a suitable sequestering agent.

In the above other, pharmaceutical composition, process, method, use and medicament manufacture features, the alternative and preferred embodiments of the compounds of the invention described herein also apply.

Antibacterial Activity :

The pharmaceutically-acceptable compounds of the present invention are useful antibacterial agents having a good spectrum of activity in vitro against standard Gram-positive organisms, which are used to screen for activity against pathogenic bacteria. Notably, the pharmaceutically-acceptable compounds of the present invention show activity against enterococci, pneumococci and methicillin resistant strains of S.aureus and coagulase

negative staphylococci, together with haemophilus and moraxella strains. The antibacterial spectrum and potency of a particular compound may be determined in a standard test system.

The (antibacterial) properties of the compounds of the invention may also be demonstrated and assessed in-vivo in conventional tests, for example by oral and/or intravenous dosing of a compound to a warm-blooded mammal using standard techniques.

The following results were obtained on a standard in-vitro test system. The activity is described in terms of the minimum inhibitory concentration (MIC) determined by the agar-dilution technique with an inoculum size of 10^4 CFU/spot. Typically, compounds are active in the range 0.01 to 256 μg/ml.

Staphylococci were tested on agar, using an inoculum of 10^4 CFU/spot and an incubation temperature of 37°C for 24 hours - standard test conditions for the expression of methicillin resistance.

Streptococci and enterococci were tested on agar supplemented with 5% defibrinated horse blood, an inoculum of 10^4 CFU/spot and an incubation temperature of 37°C in an atmosphere of 5% carbon dioxide for 48 hours - blood is required for the growth of some of the test organisms. Fastidious Gram negative organisms were tested in Mueller-Hinton broth, supplemented with hemin and NAD, grown aerobically for 24 hours at 37°C, and with an innoculum of $5x10^4$ CFU/well.

For example, the following results were obtained for the compound of Example 2:

Organism		MIC (μg/ml)
Staphylococcus aureus:	MSQS	0.5
	MRQR	0.5
Streptococcus pneumoniae		0.13
Haemophilus influenzae		4
Moraxella catarrhalis		0.5
Linezolid Resistant Streptococcus pneumoniae		1
Enterococcus faecium		0.25

MSQS = methicillin sensitive and quinolone sensitive

MRQR = methicillin resistant and quinolone resistant

Certain intermediates and/or Reference Examples described hereinafter are within the

scope of the invention and may also possess useful activity, and are provided as a further feature of the invention.

The invention is now illustrated but not limited by the following Examples in which unless otherwise stated :-

(i) evaporations were carried out by rotary evaporation in vacuo and work-up procedures were carried out after removal of residual solids by filtration;

(ii) operations were carried out at ambient temperature, that is typically in the range 18-26°C and without exclusion of air unless otherwise stated, or unless the skilled person would otherwise work under an inert atmosphere;

(iii) column chromatography (by the flash procedure) was used to purify compounds and was performed on Merck Kieselgel silica (Art. 9385) unless otherwise stated;

(iv) yields are given for illustration only and are not necessarily the maximum attainable;

(v) the structure of the end-products of the invention were generally confirmed by NMR and mass spectral techniques [proton magnetic resonance spectra were generally determined in DMSO-d_6 unless otherwise stated using a Varian Gemini 2000 spectrometer operating at a field strength of 300 MHz, or a Bruker AM250 spectrometer operating at a field strength of 250 MHz; chemical shifts are reported in parts per million downfield from tetramethysilane as an internal standard (δ scale) and peak multiplicities are shown thus: s, singlet; d, doublet; AB or dd, doublet of doublets; dt, doublet of triplets; dm, doublet of multiplets; t, triplet, m, multiplet; br, broad; fast-atom bombardment (FAB) mass spectral data were generally obtained using a Platform spectrometer (supplied by Micromass) run in electrospray and, where appropriate, either positive ion data or negative ion data were collected]; optical rotations were determined at 589nm at 20°C for 0.1M solutions in methanol using a Perkin Elmer Polarimeter 341;

(vi) each intermediate was purified to the standard required for the subsequent stage and was characterised in sufficient detail to confirm that the assigned structure was correct; purity was assessed by HPLC, TLC, or NMR and identity was determined by infra-red spectroscopy (IR), mass spectroscopy or NMR spectroscopy as appropriate;

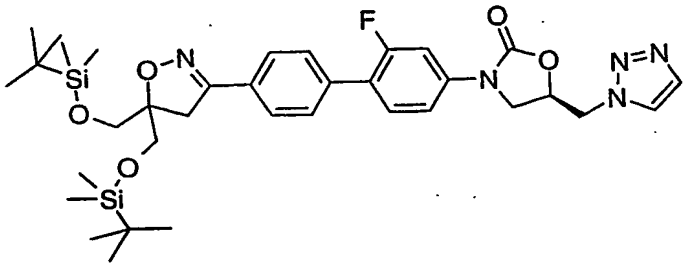
(vii) in which the following abbreviations may be used :-

DMF is N,N-dimethylformamide; DMA is N,N-dimethylacetamide; TLC is thin layer chromatography; HPLC is high pressure liquid chromatography; MPLC is medium pressure liquid chromatography; DMSO is dimethylsulfoxide; $CDCl_3$ is deuterated chloroform; MS is mass spectroscopy; ESP is electrospray; EI is electron impact; CI is chemical ionisation;

APCI is atmospheric pressure chemical ionisation; EtOAc is ethyl acetate; MeOH is methanol; phosphoryl is $(HO)_2$-P(O)-O-; phosphiryl is $(HO)_2$-P-O-; Bleach is "Clorox" 6.15% sodium hypochlorite;

(viii) temperatures are quoted as °C.

Example 1: (5*R*)-3-{4'-[5, 5-*bis*({[*tert*-Butyl(dimethyl)silyl]oxy}methyl)-4,5-dihydroisoxazol-3-yl]-2-fluoro-1,1'-biphenyl-4-yl}-5-(1*H*-1,2,3-triazol-1-ylmethyl)-1,3-oxazolidin-2-one



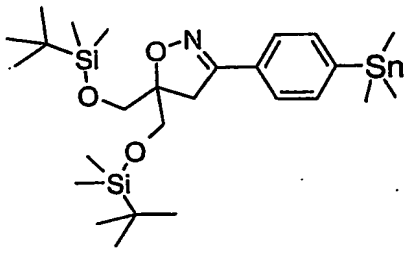
A mixture of (5*R*)-3-(3-fluoro-4-iodophenyl)-5-(1*H*-1,2,3-triazol-1-ylmethyl)-1,3-oxazolidin-2-one (388 mg, 1.00 mM), *tris*(dibenzylideneacetone)dipalladium (0) (37 mg, 0.040 mM, 0.04 equiv), and tri-2-furylphosphine (18 mg, 0.078 mM, 0.08 equiv) was degassed and then maintained under argon. Anhydrous *N*-methylpyrrolidinone (4 mL) was added to give a solution that was treated with 5,5-*bis*({[*tert*-butyl(dimethyl)silyl]oxy}methyl)-3-[4-(trimethylstannyl)phenyl]-4,5-dihydroisoxazole (718 mg, 1.20 mM) and the reaction mixture was degassed again. The reaction mixture was heated at 90 °C for *ca.* 64 hours, then allowed to cool. The cool reaction mixture was partitioned between ethyl acetate and water. The organic phase was dried ($MgSO_4$) and concentrated under vacuum to give a crude product that was purified by chromatography on silica gel [elution with 10% hexanes:ethylacetate] to give the title compound (376 mg).

MS (ESP): 696,697 (M, M+1) for $C_{35}H_{50}FN_5O_5Si_2$

NMR (DMSO-d_6) δ: 0.03 (s, 6H); 0.05 (s, 6H); 0.83 (s, 18H); 3.22 (s, 2H); 3.67-3.75 (m, 4H); 3.95 (dd, 1H); 4.28 (t, 1H); 4.85 (d, 2H); 5.18 (m, 1H); 7.38 (dd, 1H); 7.52-7.77 (m, 7H); 8.18 (s, 1H).

The intermediates for this compound were prepared as follows:

5,5-*bis*({[*tert*-Butyl(dimethyl)silyl]oxy}methyl)-3-[4-(trimethylstannyl)phenyl]-4,5-dihydroisoxazole

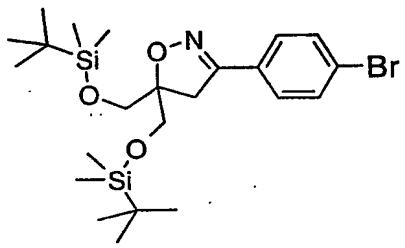


A mixture of 3-(4-bromophenyl)-5,5-bis({[*tert*-butyl(dimethyl)silyl]oxy}methyl)-4,5-dihydroisoxazole (2.80 g, 5.44 mM), bis(triphenylphosphine)palladium(II) chloride (190 mg, 0.27 mM), and 1,4-dioxane (20 mL) was degassed and then maintained under argon. The mixture was treated with hexamethylditin (2.00 g, 6.10 mM) and the reaction mixture was heated at 90 °C for *ca.* 20 hours. The reaction mixture was adsorbed onto silica gel and eluted with 10% ethyl acetate:hexanes to give the title compound (1.60 g).

MS (ESP): 598, 600 (M, M+2) for $C_{26}H_{49}NO_3Si_2Sn$

NMR (DMSO-d_6) δ: 0.05 (s, 6H); 0.07 (s, 6H); 0.28 (s, 18H); 0.86 (s, 18H); 3.19 (s, 2H); 3.68-3.74 (m, 4H); 7.55-7.61(m, 4H).

3-(4-Bromophenyl)-5,5-bis({[*tert*-butyl(dimethyl)silyl]oxy}methyl)-4,5-dihydroisoxazole

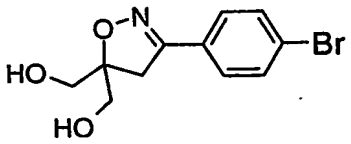


Triethylamine (2.00 mL, 14.26 mM) and then *N,N*-dimethylaminopyridine (290 mg, 2.38 mM) and then a solution of *tert*-butyldimethylsilyl chloride in dichloromethane (1.0 M, 1.31 mL, 1.31 mM) was added to a mixture of 3-(4-bromophenyl)-5,5-bis(hydroxymethyl)-4,5-dihydroisoxazole (1.70 g, 5.94 mM) and dichloromethane (20 mL). The reaction mixture was stirred at room temperature for *ca.* 16 h. The reaction was washed with water, dried over $MgSO_4$, and concentrated under vacuum. The crude material was purified by chromatography on silica gel [elution with 25% ethyl acetate:hexanes] to give the title compound (3.5 g).

MS (APCI): 514, 516 (M, M+1) for $C_{23}H_{40}BrNO_3Si_2$

NMR (DMSO-d_6) δ: 0.07 (s, 6H); 0.09 (s, 6H); 0.88 (s, 18H); 3.22 (s, 2H); 3.75 (d, 4H); 7.48-7.73 (m, 4H).

3-(4-Bromophenyl)-5,5-bis(hydroxymethyl)-4,5-dihydroisoxazole

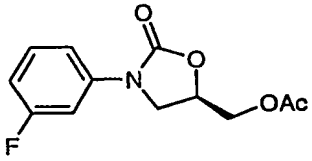


A solution of 2-methylene1,3-propanediol (2.00 g, 22.70 mM) in dichloromethane (20 mL) was treated at 0 °C with a solution of diethylzinc in hexane (1.0 M , 25.00 mL, 25.00 mM) and then slowly with a solution of 4-bromo-*N*-hydroxybenzenecarboximidoyl chloride in dichloromethane (20 mL). The reaction mixture was allowed to warm to room temperature and kept at room temperature for *ca.* 5 h. The mixture was poured into an saturated aqueous solution of ammonium chloride and extracted (twice) with dichloromethane. The combined organic phase was dried ($MgSO_4$) and concentrated under vacuum to give the title compound (2.1 g) that was used without further purification.

MS (APCI): 286, 288 (M, M+2) for $C_{11}H_{12}BrNO_3$

NMR (DMSO-d_6) δ: 3.28 (s, 2H); 3.49 (d, 4H); 5.02 (t, 2H); 7.59-7.67 (m, 4H).

Acetic acid (5*R*)-3-(3-fluorophenyl)-1,3-oxazolidin-2-on-5-ylmethyl ester

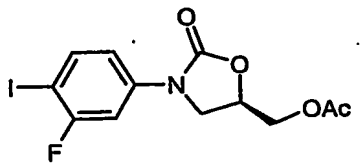


(5*R*)-3-(3-Fluorophenyl)-5-hydroxymethyl-1,3-oxazolidin-2-one (40 g, 0.189 M, see Upjohn WO 94-13649) was suspended by stirring in dry dichloromethane (400 mL) under nitrogen. Triethylamine (21 g, 0.208 M) and 4-dimethylaminopyridine (0.6 g, 4.9 mM) were added, followed by dropwise addition of acetic anhydride (20.3 g, 0.199 M) over 30 minutes, and stirring continued at ambient temperature for 18 hours. Saturated aqueous sodium bicarbonate (250 mL) was added, the organic phase separated, washed with 2% sodium dihydrogen phosphate, dried (magnesium sulfate), filtered and evaporated to give the desired product (49.6 g) as an oil.

MS (ESP): 254 (MH^+) for $C_{12}H_{12}FNO_4$

NMR ($CDCl_3$) δ: 2.02 (s, 3H); 3.84 (dd, 1H); 4.16 (t, 1H); 4.25 (dd, 1H); 4.32 (dd, 1H); 4.95 (m, 1H); 6.95 (td, 1H); 7.32 (d, 1H); 7.43 (t, 1H) ; 7.51 (d, 1H).

Acetic acid (5*R*)-3-(3-fluoro-4-iodo-phenyl)-1,3-oxazolidin-2-one-5-ylmethyl ester

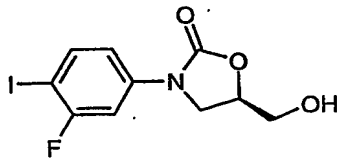


Acetic acid (5*R*)-3-(3-fluoro-phenyl)-1,3-oxazolidin-2-one-5-ylmethyl ester (15.2 g, 60 mM) was dissolved in a mixture of chloroform (100 mL) and acetonitrile (100 mL) under nitrogen, and silver trifluoroacetate (16.96 g, 77 mM) added. Iodine (18.07 g, 71 mM) was added in portions over 30 minutes to the vigorously stirred solution, and stirring continued at ambient temperature for 18 hours. As reaction was not complete, a further portion of silver trifluoroacetate (2.64 g, 12 mM) was added and stirring continued for 18 hours. After filtration, the mixture was added to sodium thiosulfate solution (3%, 200 mL) and dichloromethane (200 mL), and the organic phase separated, washed with sodium thiosulfate (200 mL), saturated aqueous sodium bicarbonate (200 mL), brine (200 mL), dried (magnesium sulfate), filtered and evaporated. The crude product was suspended in *iso*hexane (100 mL), and sufficient diethyl ether added to dissolve out the brown impurity while stirring for 1 hour. Filtration gave the desired product (24.3 g) as a cream solid.

MS (ESP): 380 (MH^+) for $C_{12}H_{11}FINO_4$

NMR (DMSO-d_6) δ: 2.03 (s, 3H); 3.82 (dd, 1H); 4.15 (t, 1H); 4.24 (dd, 1H); 4.30 (dd, 1H); 4.94 (m, 1H); 7.19 (dd, 1H); 7.55 (dd, 1H); 7.84 (t, 1H).

(5*R*)-3-(3-Fluoro-4-iodophenyl)-5-hydroxymethyl-1,3-oxazolidin-2-one



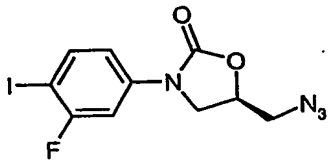
Acetic acid (5*R*)-3-(3-fluoro-4-iodophenyl)-1,3-oxazolidin-2-one-5-ylmethyl ester (30 g, 79 mM) was treated with potassium carbonate (16.4 g, 0.119 mM) in a mixture of methanol (800 mL) and dichloromethane (240 mL) at ambient temperature for 25 minutes, then immediately neutralised by the addition of acetic acid (10 mL) and water (500 mL). The precipitate was filtered, washed with water, and dissolved in dichloromethane (1.2 L), the solution washed

with saturated sodium bicarbonate, and dried (magnesium sulfate). Filtration and evaporation gave the desired product (23 g).

MS (ESP): 338 (MH^+) for $C_{10}H_9FINO_3$

NMR (DMSO-d_6) δ: 3.53 (m, 1H); 3.67 (m, 1H); 3.82 (dd, 1H); 4.07 (t, 1H); 4.70 (m, 1H); 5.20 (t, 1H); 7.21 (dd, 1H); 7.57 (dd, 1H); 7.81 (t, 1H).

(5*R*)-5-Azidomethyl-3-(3-fluoro-4-iodophenyl)-1,3-oxazolidin-2-one

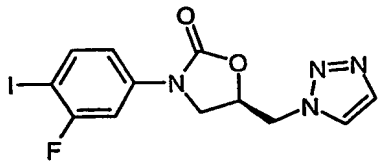


Methanesulfonyl chloride (17.9 mL) was added dropwise to a stirred solution of (5*R*)-3-(3-fluoro-4-iodophenyl)-5-hydroxymethyl-1,3-oxazolidin-2-one (55.8 g) and triethylamine (46.1 mL) in dry dichloromethane (800 mL) under an atmosphere of dry nitrogen and maintained below room temperature by an ice-bath. The stirred reaction mixture was allowed to warm to room temperature during 3 hours and then washed sequentially with water and brine and then dried (Na_2SO_4). Solvent was removed under reduced pressure to give the intermediate mesylate as a yellow solid (68 g) that was used without further purification.

A stirred solution in DMF (800 mL) of a mixture of the intermediate mesylate (68 g) and sodium azide (32.3 g) was heated at 75°C overnight. The mixture was allowed to cool to room temperature, diluted with water, and extracted twice with ethyl acetate. The combined extracts were washed sequentially with water and brine, and then dried (Na_2SO_4). Solvent was removed under reduced pressure to give a yellow oil that was purified by column chromatography on silica-gel [elution with ethyl acetate:hexanes (1:1)] to give the product azide as an off-white solid (49 g). The product could be further purified by trituration with ethyl acetate/hexanes.

^{1}H-NMR (DMSO-d_6) δ: 3.57-3.64 (dd, 1H); 3.70-3.77 (dd, 1H); 3.81-3.87 (dd, 1H); 4.06 (t, 1H); 4.78-4.84 (m, 1H); 7.05-7.09 (ddd, 1H); 7.45 (dd, 1H); 7.68-7.74 (dd, 1H).

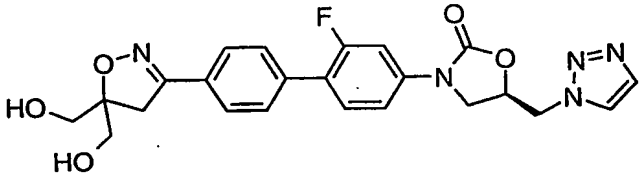
(5*R*)-3-(3-Fluoro-4-iodophenyl)-5-(1*H*-1,2,3-triazol-1-ylmethyl)-1,3-oxazolidin-2-one



A stirred solution in dioxan (300 mL) of a mixture of the (5*R*)-5-azidomethyl-3-(3-fluoro-4-iodophenyl)-1,3-oxazolidin-2-one (30 g) and bicyclo[2.2.1]heptadiene (30 mL) was heated under reflux overnight. The mixture was allowed to cool to room temperature and then evaporated to dryness under reduced pressure to give a brown solid. The brown solid was purified by column chromatography on silica-gel [elution with a gradient from 98:2 to 95:5 methanol:chloroform] to give the product triazole as a pale yellow solid (20 g). The product could be further purified by trituration with dichloromethane/hexanes (1:1) to give an off-white solid.

^{1}H-NMR (DMSO-d_6) δ: 3.86-3.92 (dd, 1H); 4.23 (t, 1H); 4.83 (d, 2H); 5.11-5.19 (m, 1H); 7.12-7.16 (dd, 1H); 7.47-7.51 (dd, 1H); 7.76 (s, 1H); 7.79-7.85 (dd, 1H); 8.16 (s, 1H).

Example 2: (5*R*)-3-{4'-(5, 5-*bis*(Hydroxymethyl)-4,5-dihydroisoxazol-3-yl]-2-fluoro-1,1'-biphenyl-4-yl}-5-(1*H*-1,2,3-triazol-1-ylmethyl)-1,3-oxazolidin-2-one

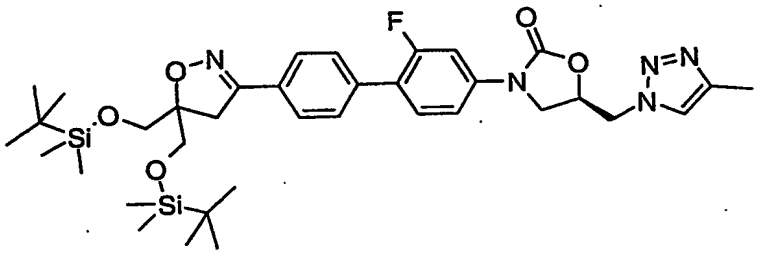


A solution of tetrabutylammonium fluoride (TBAF) in THF (1.0 M, 1.62 mL, 1.62 mM) was added to a solution of (5*R*)-3-{4'-[5, 5-*bis*({[*tert*-butyl(dimethyl)silyl]oxy}methyl)-4,5-dihydroisoxazol-3-yl]-2-fluoro-1,1'-biphenyl-4-yl}-5-(1*H*-1,2,3-triazol-1-ylmethyl)-1,3-oxazolidin-2-one (376 mg, 0.54 mM) in THF (4 mL). The reaction mixture was stirred at room temperature for 3 h and then water was added. The mixture was extracted with ethyl acetate and the organic phase dried ($MgSO_4$) and concentrated under vacuum. The crude product was purified by chromatography on silica gel [elution with 5% methanol:ethyl acetate] to give the title compound (116 mg).

MS (ESP): 468 (M+1) for $C_{23}H_{22}FN_5O_5$

NMR (DMSO-d_6) δ: 3.27 (s, 2H); 3.51 (d, 4H); 3.97 (dd, 1H); 4.30 (t, 1H); 4.87 (d, 2H); 5.03 (t, 2H); 5.19 (m, 1H); 7.39 (dd, 1H); 7.53-7.78 (m, 7H); 8.19 (s, 1H).

Example 3: (5*R*)-3-{4'-[5, 5-*bis*({[*tert*-Butyl(dimethyl)silyl]oxy}methyl)-4,5-dihydroisoxazol-3-yl]-2-fluoro-1,1'-biphenyl-4-yl}-5-[(4-methyl-1*H*-1,2,3-triazol-1-yl)methyl]-1,3-oxazolidin-2-one



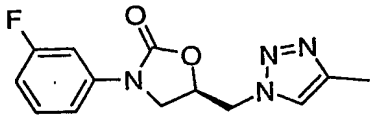
The title compound was prepared from 5,5-bis({[*tert*-butyl(dimethyl)silyl]oxy}methyl)-3-[4-(trimethylstannyl)phenyl]-4,5-dihydroisoxazole (900 mg, 1.50 mM) and (5*R*)-3-(3-fluoro-4-iodophenyl)-5-[(4-methyl-1*H*-1,2,3-triazol-1-yl)methyl]-1,3-oxazolidin-2-one (402 mg, 1.00 mM) using essentially the same procedure as that described for Example 1, (200 mg).

MS (ESP): 710, 711 (M, M+1) for $C_{36}H_{52}FN_5O_5Si_2$

NMR (DMSO-d_6) δ: 0.03 (s, 6H); 0.05 (s, 6H); 0.83 (18 H); 2.22 (s, 3H); 3.22 (s, 2H); 3.67-3.75 (m, 4H); 3.93 (dd, 1H); 4.27 (t, 1H); 4.75 (d, 2H); 5.13 (m, 1H); 7.39 (dd, 1H); 7.53-7.75 (m, 6H); 7.87 (s, 1H).

The intermediates for this compound were prepared as follows:

(5*R*)-3-(3-Fluorophenyl)-5-[(4-methyl-1*H*-1,2,3-triazol-1-yl)methyl]-1,3-oxazolidin-2-one

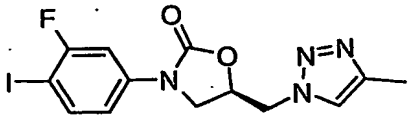


A stirred solution of *N, N*-diisopropylethylamine (3.20 mL, 18.35 mM) and (5*S*)-5-(aminomethyl)-3-(3-fluorophenyl)-1,3-oxazolidin-2-one (0.77 g, 3.57 mM, see Dong Pharmaceuticals WO 0194342) in anhydrous methanol (25 mL) was treated at 0 °C with *N'*-[2,2-dichloro-1-methylethylidene]-4-methylbenzenesulfonohydrazide (1.28 g, 4.58 mM). The reaction mixture was allowed to warm and stirred at room temperature overnight. The reaction mixture was then concentrated under vacuum to give a crude product was purified by chromatography on silica gel [elution with 2% methanol:dichloromethane] to give the title compound (0.71g).

MS (ESP): 277 (M+1) for $C_{13}H_{13}FN_4O_2$

NMR (DMSO-d_6) δ: 2.24 (s, 3H); 3.90 (dd, 1H); 4.25 (t, 1H); 4.77 (d, 2H); 5.13 (m, 1H); 6.99 (m, 1H); 7.28 (d, 1H); 7.42-7.48 (m, 2H); 7.89 (s, 1H).

(5*R*)-3-(3-Fluoro-4-iodophenyl)-5-[(4-methyl-1*H*-1,2,3-triazol-1-yl)methyl]-1,3-oxazolidin-2-one

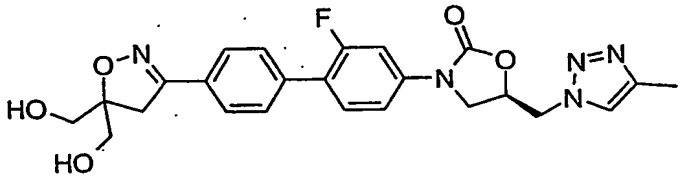


Iodine (0.55 g, 2.17 mM) was added over 1.5 h to a mixture of silver trifluoroacetate (0.52 g, 2.35 mM) and a solution of (5*R*)-3-(3-fluorophenyl)-5-[(4-methyl-1*H*-1,2,3-triazol-1-yl)methyl]-1,3-oxazolidin-2-one (0.50 g, 1.81 mM) in dichloromethane (15 mL). The reaction mixture was stirred overnight and then the precipitated solids were isolated from the reaction mixture by filtration. The filtrate was treated with additional portions of silver trifluoroacetate (0.38 g, 1.72 mM) and iodine (0.27 g, 1.06 mM), and refiltered after an additional 24 h. The retained solid from the filtrations was extracted with methanol and the methanol extract was concentrated under vacuum to give the title compound (0.31g).

MS (ESP): 403 (M+1) for $C_{13}H_{12}FIN_4O_2$

NMR (DMSO-d_6) δ: 2.24 (s, 3H); 3.89 (dd, 1H); 4.23 (t, 1H); 4.76 (d, 2H); 5.12 (m, 1H); 7.17 (dd, 1H); 7.51 (dd, 1H); 7.84 (t, 1H); 7.88 (s, 1H).

Example 4: (5*R*)-3-{4'-5, 5-*bis*(Hydroxymethyl)-4,5-dihydroisoxazol-3-yl]-2-fluoro-1,1'-biphenyl-4-yl}-5-[(4-methyl-1*H*-1,2,3-triazol-1-yl)methyl]-1,3-oxazolidin-2-one

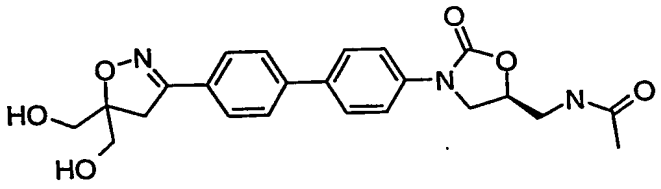


The title compound was obtained from (5*R*)-3-{4'-[5, 5-*bis*({[*tert*-butyl(dimethyl)silyl]oxy}methyl)-4,5-dihydroisoxazol-3-yl]-2-fluoro-1,1'-biphenyl-4-yl}-5-[(4-methyl-1*H*-1,2,3-triazol-1-yl)methyl]-1,3-oxazolidin-2-one (200 mg, 0.28 mM) using essentially the same procedure as that desribed for Example 1, (49 mg)

MS (ESP): 482 (M+1) for $C_{24}H_{24}FN_5O_5$

NMR (DMSO-d_6) δ: 2.23 (s, 3H); 3.26-3.33 (2H, overlapping with H_2O peak); 3.51(d, 4H); 3.94(dd, 1H); 4.28 (t, 1H); 4.78 (d, 2H); 5.04 (t, 2H); 5.14 (m, 1H); 7.40 (dd, 1H); 7.54-7.77 (m, 6H); 7.89 (s, 1H).

Example 5: *N*-[((5*S*)-3-{4'-[5,5-*bis*(Hydroxymethyl)-4,5-dihydroisoxazol-3-yl]-1,1'-biphenyl-4-yl}-2-oxo-1,3-oxazolidin-5-yl)methyl]acetamide



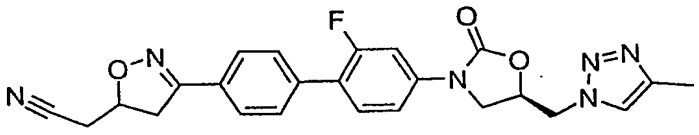
The title compound was obtained from (5*S*)-3-{4'-[5, 5-*bis*({[*tert*-butyl(dimethyl)silyl]oxy}methyl)-4,5-dihydroisoxazol-3-yl]-2-fluoro-1,1'-biphenyl-4-yl}-5-acetamidomethyl)-1,3-oxazolidin-2-one using essentially the same procedure as Example 2 (93 mg).

MS (ESP): 440, 441 (M, M+1) for $C_{23}H_{25}N_3O_6$

NMR (DMSO-d_6) δ: 1.84 (s, 3H); 3.26 (s, 2H); 3.44 (t, 2H); 3.51 (d, 4H); 3.80 (dd, 1H); 4.18 (t, 1H); 4.75 (m, 1H); 5.03 (t, 2H); 7.64-7.80 (m, 8H); 8.28 (t, 1H).

The starting material for this compound were prepared from (5*S*)-3-(3-fluoro-4-iodophenyl)-5-(acetamidomethyl)-1,3-oxazolidin-2-one and 3-(4-bromophenyl)-5,5-bis({[*tert*-butyl(dimethyl)silyl]oxy}methyl)-4,5-dihydroisoxazole using essentially the same procedure as that described for Example 1

Example 6: [3-(2'-Fluoro-4'-{(5*R*)-5-[(4-methyl-1*H*-1,2,3-triazol-1-yl)methyl]-2-oxo-1,3-oxazolidin-3-yl}-1,1'-biphenyl-4-yl)-4,5-dihydroisoxazol-5-yl]acetonitrile



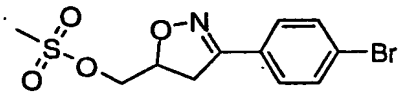
The title compound was obtained from (5*R*)-3-[3-fluoro-4-(trimethylstannyl)phenyl]-5-[(4-methyl-1*H*-1,2,3-triazol-1-yl)methyl]-1,3-oxazolidin-2-one (0.98 g, 2.23 mM) and [3-(4-bromophenyl)-4,5-dihydroisoxazol-5-yl]acetonitrile (0.40 g, 1.51 mM) using essentially the same procedure as that described for Example 1, (30 mg).

MS (ESP): 461 (M+1) for $C_{24}H_{21}FN_6O_3$

NMR (DMSO-d_6) δ: 2.22 (s, 3H); 2.97 (dd, 2H); 3.22-3.27 (m overlapping with H_2O, 1H); 3.68 (dd, 1H); 3.93 (dd, 1H); 4.27 (t, 1H); 4.77 (d, 2H); 5.03 (m, 1H); 5.13 (m, 1H); 7.39 (dd, 1H); 7.53-7.79 (m, 6H); 7.87 (s, 1H).

The intermediates for this compound were prepared as follows:

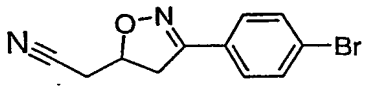
[3-(4-Bromophenyl)-4,5-dihydroisoxazol-5-yl]methyl methanesulfonate



A solution of [3-(4-bromophenyl)-4,5-dihydroisoxazol-5-yl]-methanol (84.30 g, 0.33 M) (AstraZeneca WO 01/40222 A1) in anhydrous dichloromethane (500 mL) was maintained at 0 °C and treated with triethylamine (64.10 mL, 0.46 M) and then dropwise methanesulfonyl chloride (30.65 mL, 0.40 M). The reaction mixture was stirred for 2 hours at 0°C and then treated with aqueous sodium bicarbonate (200 mL). The phases were separated and the aqueous phase was extracted with dichloromethane (2 x 200 mL). The organic phases were combined, dried (sodium sulfate) and concentrated *in vacuo* to give the title compound (110 g) sufficiently pure for further use.

NMR (DMSO-d_6) δ: 3.08 (s, 3H); 3.27 (dd, 1H); 3.47 (dd, 1H); 4.37 (m, 2H); 5.02 (m, 1H); 7.53 (m, 4H).

[3-(4-Bromophenyl)-4,5-dihydroisoxazol-5-yl]acetonitrile

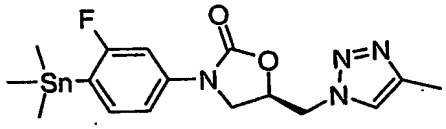


A mixture of [3-(4-bromophenyl)-4,5-dihydroisoxazol-5-yl]methyl methanesulfonate (0.50 g, 1.50 mM), sodium cyanide (0.15 g, 3.00 mM), and *N,N*-dimethylformamide was heated at 75 °C for *ca.* 16 h. The reaction mixture was diluted with ethyl acetate and the washed with water. The organic phase was dried ($MgSO_4$) and concentrated under vacuum to give the title compound (0.40 g) sufficiently pure for further use.

MS (ESP): 265, 267 (M, M+2) for $C_{11}H_9BrN_2O$

NMR (DMSO-d_6) δ: 2.94-2.97 (m, 2H); 3.21 (dd, 1H); 3.63 (dd, 1H); 5.00 (m, 1H); 7.60-7.68 (m, 4H).

(5*R*)-3-[3-Fluoro-4-(trimethylstannyl)phenyl]-5-[(4-methyl-1*H*-1,2,3-triazol-1-yl)methyl]-1,3-oxazolidin-2-one

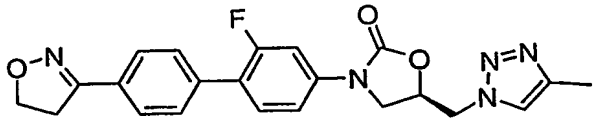


A mixture of (5*R*)-3-(3-fluoro-4-iodophenyl)-5-[(4-methyl-1*H*-1,2,3-triazol-1-yl)methyl]-1,3-oxazolidin-2-one (5.12 g, 12.70 mM) and bis(triphenylphospine)palladium(II) chloride (0.45 g, 0.05 mM) was degassed and maintained under argon. The reaction mixture was treated with dioxane (50 mL) and then with hexamethylditin (5.00g, 15.30 mM) and the reaction was degassed again and maintained under argon. The reaction mixture was heated at 90° for 20 hours. The cool reaction mixture was adsorbed onto silica-gel, and purified by flash chromatography [elution with a gradient from 50 % hexanes:ethyl acetate to 100%ethyl acetate] to give the title compound (3.91 g).

MS (ESP): 440 (MH^+) for $C_{16}H_{21}FN_4O_2Sn$

NMR (DMSO-d_6) δ: 0.09 (t, 9H); 2.00 (s, 3H); 3.65 (dd, 1H); 4.00 (t, 1H); 4.53 (d, 2H); 4.88 (m, 1H); 7.03 (dd, 1H); 7.11 (dd, 1H); 7.18 (dd, 1H); 7.64 (s, 1H).

Example 7: (5*R*)-3-[4'-(4,5-dihydroisoxazol-3-yl)-2-fluoro-1,1'-biphenyl-4-yl]-5-[(4-methyl-1*H*-1,2,3-triazol-1-yl)methyl]-1,3-oxazolidin-2-one



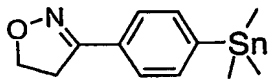
The title compound was prepared from (5*R*)-3-(3-fluoro-4-iodophenyl)-5-[(4-methyl-1*H*-1,2,3-triazol-1-yl)methyl]-1,3-oxazolidin-2-one (603 mg, 1.50 mM) and 3-[4-(trimethylstannyl)phenyl]-4,5-dihydroisoxazole (558 mg, 1.80 mM) using essentially the same procedure as that used for Example 1, (394 mg).

MS (ESP): 422 (M+1) for $C_{22}H_{20}FN_5O_3$

NMR (DMSO-d_6) δ: 2.22 (s, 3H); 3.41 (t, 2H); 3.92 (dd, 1H); 4.27 (t, 1H); 4.40 (t, 2H); 4.77 (d, 2H); 5.13 (m, 1H); 7.39 (dd, 1H); 7.53-7.81 (m, 6H); 7.88 (s, 1H).

The intermediate for this compound was prepared as follows:

3-[4-(Trimethylstannyl)phenyl]-4,5-dihydroisoxazole

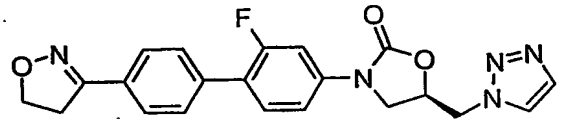


A solution of 3-(4-bromophenyl)-4,5-dihydroisoxazole (1.40 g, 6.19 mM) in 1,4-dioxane (30 mL) (F. L. Scott; A. F. Hagarty, R..J. MacConaill, *Tetrahedron Lett.*, **1972,** *13,* 1213) was treated with bis(triphenylphosphine)palladium(II) chloride (217 mg, 0.31 mM) and the solution was degassed and maintained under argon. The mixture was treated with hexamethylditin (3.00g, 9.16 mM) and the reaction mixture was heated at 90 °C for *ca.* 20 hours. The reaction mixture was adsorbed onto silica-gel and purified by chromatography [elution with a gradient from 5% to 10% ethyl acetate:hexanes] to give the title compound (1.70 g).

MS APCI: 310, 312 (M, M+2) for $C_{12}H_{17}NOSn$

NMR (DMSO-d_6) δ: 0.27 (s, 9H); 3.29-3.38 (m, 2H overlapping with H_2O); 4.36 (t, 2H); 7.54-7.63) m, 4H).

Example 8: (5*R*)-3-[4'-(4,5-dihydroisoxazol-3-yl)-2-fluoro-1,1'-biphenyl-4-yl]-5-(1*H*-1,2,3-triazol-1-ylmethyl)-1,3-oxazolidin-2-one



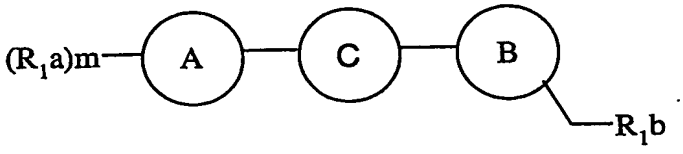
The title compound was prepared from (5*R*)-3-(3-fluoro-4-iodophenyl)-5-(1*H*-1,2,3-triazol-1-ylmethyl)-1,3-oxazolidin-2-one (582 mg, 1.50 mM) and 3-[4-(trimethylstannyl)phenyl]-4,5-dihydroisoxazole (558 mg, 1.80 mM) using essentially the same procedure as that used for Example 1,(176 mg).

MS APCI: 408 (M+1) for $C_{21}H_{18}FN_5O_3$

NMR (DMSO-d_6) δ: 3.41 (t, 2H); 3.95 (dd, 1H); 4.29 (t, 1H); 4.40 (t, 2H); 4.86 (d, 2H); 5.18 (m, 1H); 7.38 (dd, 1H); 7.52-7.78 (m, 7H); 8.18 (s, 1H).

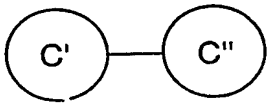
Claims

1. A compound of the formula (I), or a pharmaceutically-acceptable salt, or an in-vivo-hydrolysable ester thereof,

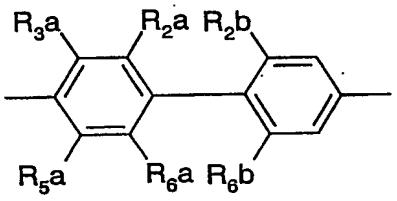


(I)

wherein in (I) C is a biaryl group C'-C''



where C' and C'' are independently aryl or heteroaryl rings such that the group C is represented by any one of the groups D to O below:



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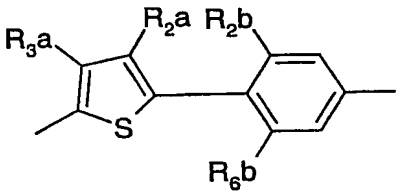

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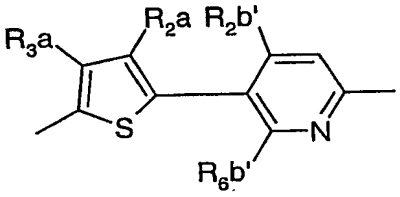

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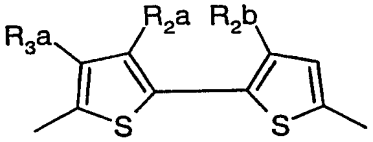

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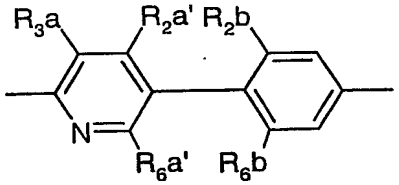

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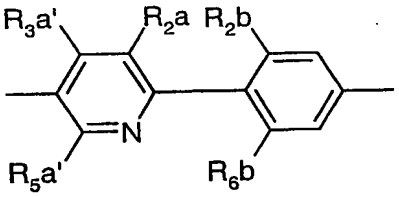
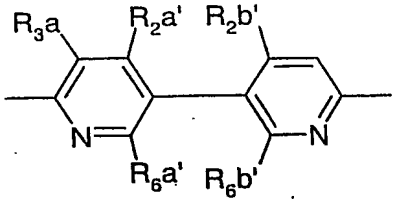


I



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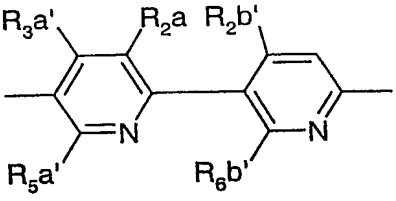

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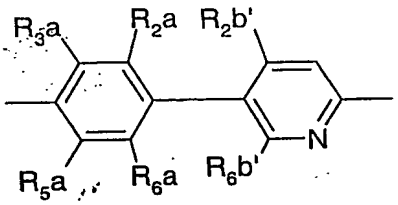
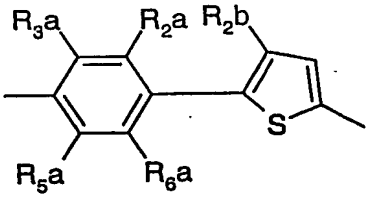
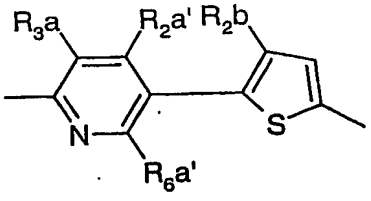


L



M



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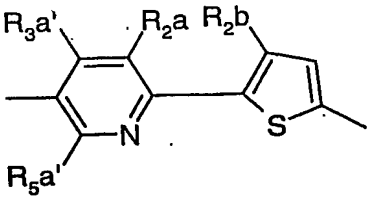
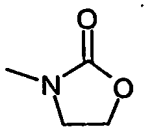


O

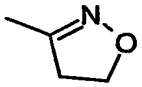
wherein the groups D to O are attached to rings A and B in the orientation [(A-C') and (C''-B)] shown;

wherein A and B are independently selected from

i) ii)



and



wherein A is linked as shown in (I) via the 3-position to ring C' of group C and independently substituted in the 4 and 5 positions as shown in (I) by one or more substituents $-(R_1a)m$;

and wherein B is linked as shown in (I) via the 3-position to ring C'' of group C and independently substituted in the 5 position as shown in (I) by substituent $-CH_2-R_1b$;

R_2b and R_6b are independently selected from H, F, Cl, OMe, Me, Et and CF_3;

R_2b' and R_6b' are independently selected from H, OMe, Me, Et and CF_3;

R_2a and R_6a are independently selected from H, Br; F, Cl, OMe, SMe; Me, Et and CF_3;

R_2a' and R_6a' are independently selected from H, OMe, SMe; Me, Et and CF_3;

R_3a and R_5a are independently selected from H, (1-4C)alkyl, Br, F, Cl, OH, (1-4C)alkoxy, $-S(O)_n$(1-4C)alkyl (wherein n = 0,1,or 2), amino, (1-4C)alkylcarbonylamino-, nitro, cyano, -CHO, -CO(1-4C) alkyl, $-CONH_2$ and -CONH(1-4C)alkyl;

R_3a', R_5a' are independently selected from H, (1-4C)alkyl, OH, (1-4C)alkoxy, (1-4C)alkylthio, amino, (1-4C)alkylcarbonylamino-, nitro, cyano, -CHO, -CO(1-4C)alkyl, $-CONH_2$ and -CONH(1-4C)alkyl;

wherein one of R_3a, R_5a, R_3a', R_5a'taken together with a substituent R_1a at position 4 of ring A and rings A and C' may form a 5-7 membered ring;

wherein any (1-4C)alkyl group may be optionally substituted with F, OH, (1-4C)alkoxy, $-S(O)_n$(1-4C)alkyl (wherein n = 0,1,or 2) or cyano;

wherein when ring C' is a pyridine ring (ie when group C is group H, I, J, K, N or O) the ring nitrogen may optionally be oxidised to an N-oxide;

R_1a is independently selected from R_1a1 to R_1a4 below:

R_1a1: AR1, AR2, AR2a, AR2b, AR3, AR3a, AR3b, AR4, AR4a, CY1, CY2;

R_1a2: cyano, carboxy, (1-4C)alkoxycarbonyl, -C(=W)NRvRw [wherein W is O or S, Rv and Rw are independently H, or (1-4C)alkyl and wherein Rv and Rw taken together with the amide or thioamide nitrogen to which they are attached can form a 5-7 membered ring

optionally with an additional heteroatom selected from N, O, S(O)n in place of 1 carbon atom of the so formed ring; wherein when said ring is a piperazine ring, the ring may be optionally substituted on the additional nitrogen by a group selected from (1-4C)alkyl, (1-4C)cycloalkyl, (1-4C)acyl, -COO(1-4C)alkyl, S(O)n(1-4C)alkyl (wherein n = 1 or 2), -COOAR1, -CS(1-4C)alkyl) and –C(=S)O(1-4C)alkyl; wherein any (1-4C)alkyl, (1-4C)acyl and (1-4C)cycloalkyl substituent may itself be substituted by cyano, hydroxy or halo, provided that, such a substituent is not on a carbon adjacent to a nitrogen atom of the piperazine ring], ethenyl, 2-(1-4C)alkylethenyl, 2-cyanoethenyl, 2-cyano-2-((1-4C)alkyl)ethenyl, 2-nitroethenyl, 2-nitro-2-((1-4C)alkyl)ethenyl, 2-((1-4C)alkylaminocarbonyl)ethenyl, 2-((1-4C)alkoxycarbonyl)ethenyl, 2-(AR1)ethenyl, 2-(AR2)ethenyl, 2-(AR2a)ethenyl;

R_1a3: (1-10C)alkyl

{optionally substituted by one or more groups (including geminal disubstitution) each independently selected from hydroxy, (1-10C)alkoxy, (1-4C)alkoxy-(1-4C)alkoxy, (1-4C)alkoxy-(1-4C)alkoxy-(1-4C)alkoxy, (1-4C)alkylcarbonyl, phosphoryl [-O-P(O)$(OH)_2$, and mono- and di-(1-4C)alkoxy derivatives thereof], phosphiryl [-O-P$(OH)_2$ and mono- and di-(1-4C)alkoxy derivatives thereof], and amino; and/or optionally substituted by one group selected from carboxy, phosphonate [phosphono, -P(O)$(OH)_2$, and mono- and di-(1-4C)alkoxy derivatives thereof], phosphinate [-P$(OH)_2$ and mono- and di-(1-4C)alkoxy derivatives thereof], cyano, halo, trifluoromethyl, (1-4C)alkoxycarbonyl, (1-4C)alkoxy-(1-4C)alkoxycarbonyl, (1-4C)alkoxy-(1-4C)alkoxy-(1-4C)alkoxycarbonyl, (1-4C)alkylamino, di((1-4C)alkyl)amino, (1-6C)alkanoylamino-, (1-4C)alkoxycarbonylamino-, N-(1-4C)alkyl-N-(1-6C)alkanoylamino-, -C(=W)NRvRw [wherein W is O or S, Rv and Rw are independently H, or (1-4C)alkyl and wherein Rv and Rw taken together with the amide or thioamide nitrogen to which they are attached can form a 5-7 membered ring optionally with an additional heteroatom selected from N, O, S(O)n in place of 1 carbon atom of the so formed ring; wherein when said ring is a piperazine ring, the ring may be optionally substituted on the additional nitrogen by a group selected from (1-4C)alkyl, (1-4C)cycloalkyl, (1-4C)acyl, -COO(1-4C)alkyl, S(O)n(1-4C)alkyl (wherein n = 1 or 2), -COOAR1, -CS(1-4C)alkyl and –C(=S)O(1-4C)alkyl], (=NORv) wherein Rv is as hereinbefore defined, (1-4C)alkylS$(O)_p$NH-, (1-4C)alkylS$(O)_p$-((1-4C)alkyl)N-, fluoro(1-4C)alkylS$(O)_p$NH-, fluoro(1-4C)alkylS$(O)_p$((1-4C)alkyl)N-, (1-4C)alkylS$(O)_q$-, CY1, CY2, AR1, AR2, AR3, AR1-O-, AR2-O-, AR3-O-, AR1-S$(O)_q$- , AR2-S$(O)_q$- , AR3-S$(O)_q$- , AR1-NH-, AR2-NH-, AR3-NH- (p is 1 or 2 and q is 0, 1 or 2), and also AR2a, AR2b, AR3a and AR3b versions of

AR2 and AR3 containing groups}; wherein any (1-4C)alkyl, (1-4C)acyl and (1-4C)cycloalkyl present in any substituent on R_1a3 may itself be substituted by one or two groups selected from cyano, hydroxy, halo, amino, (1-4C)alkylamino and di(1-4C)alkylamino , provided that such a substituent is not on a carbon adjacent to a heteroatom atom if present;

R_1a4: $R^{14}C(O)O(1\text{-}6C)$alkyl wherein R^{14} is AR1, AR2, AR2a, AR2b, (1-4C)alkylamino, benzyloxy-(1-4C)alkyl or (1-10C)alkyl {optionally substituted as defined for (R_1a3);

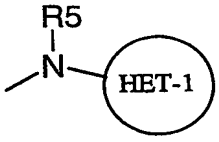
m is 0, 1 or 2;

wherein two substituents R_1a both at the 4 or 5 position of ring A taken together may form a 5 to 7 membered spiro ring;

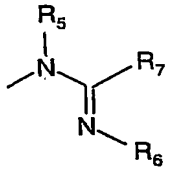
wherein two substituents R_1a at the 4 and 5 positions of ring A taken together may form a 5 to 7 membered fused ring;

provided that if (R_1a)m is a single substituent R_1a at the 5 position of ring A then R_1a is not $-CH_2X$ wherein X is selected from R1b;

R_1b is independently selected from hydroxy, -OSi(tri-(1-6C)alkyl) (wherein the 3 (1-6C)alkyl groups are independently selected from all possible (1-6C)alkyl groups), $-NR_5C(=W)R_4$, $-OC(=O)R_4$,

a) 

, b) 

and c) 

wherein W is O or S;

provided that if group C is group H or group I, and if one of substituents R_2b and R_6b is H and the other is F, and if all of substituents R_2a, R_6a, R_2a', R_6a', R_3a, R_5a, R_3a', R_5a' are H at each occurrence,then R_1b is not –NHC(=O)Me;

R_4 is hydrogen, amino, (1-8C)alkyl, $-NHR_{12}$, $-N(R_{12})(R_{13})$, $-OR_{12}$ or $-SR_{12}$, (2-4C)alkenyl, -(1-8C)alkylaryl, mono-, di-, tri- and per-halo(1-8C)alkyl, $-(CH_2)p$(3-6C)cycloalkyl or $-(CH_2)p$(3-6C)cycloalkenyl wherein p is 0, 1 or 2;

R_5 is hydrogen, (3-6C)cycloalkyl, phenyloxycarbonyl, tert-butoxycarbonyl, fluorenyloxycarbonyl, benzyloxycarbonyl, (1-6C)alkyl (optionally substituted by cyano or (1-4C)alkoxycarbonyl), $-CO_2R_8$, $-C(=O)R_8$, $-C(=O)SR_8$, $-C(=S)R_8$, $P(O)(OR_9)(OR_{10})$ and $-SO_2R_{11}$, wherein R_8, R_9, R_{10} and R_{11} are as defined hereinbelow;

HET-1 is selected from HET-1A and HET-1B wherein:

HET-1A is a C-linked 5-membered heteroaryl ring containing 2 to 4 heteroatoms independently selected from N, O and S; which ring is optionally substituted on a C atom by an oxo or thioxo group; and/or which ring is optionally substituted on any available C atom by one or two substituents selected from RT as hereinafter defined and/or on an available nitrogen atom, (provided that the ring is not thereby quaternised) by (1-4C)alkyl;

HET-1B is a C-linked 6-membered heteroaryl ring containing 2 or 3 nitrogen heteroatoms, which ring is optionally substituted on a C atom by an oxo or thioxo group; and/or which ring is optionally substituted on any available C atom by one, two or three substituents selected from RT as hereinafter defined and/or on an available nitrogen atom, (provided that the ring is not thereby quaternised) by (1-4C)alkyl;

HET-2 is selected from HET-2A and HET-2B wherein

HET- 2A is an N-linked 5-membered, fully or partially unsaturated heterocyclic ring, containing either (i) 1 to 3 further nitrogen heteroatoms or (ii) a further heteroatom selected from O and S together with an optional further nitrogen heteroatom; which ring is optionally substituted on a C atom, other than a C atom adjacent to the linking N atom, by an oxo or thioxo group; and/or which ring is optionally substituted on any available C atom, other than a C atom adjacent to the linking N atom, by a substituent selected from RT as hereinafter defined and/or on an available nitrogen atom, other than a N atom adjacent to the linking N atom, (provided that the ring is not thereby quaternised) by (1-4C)alkyl;

HET-2B is an N-linked 6-membered di-hydro-heteroaryl ring containing up to three nitrogen heteroatoms in total (including the linking heteroatom), which ring is substituted on a suitable C atom, other than a C atom adjacent to the linking N atom, by oxo or thioxo and/or which ring is optionally substituted on any available C atom, other than a C atom adjacent to the linking N atom, by one or two substituents independently selected from RT as hereinafter defined and/or on an available nitrogen atom, other than a N atom adjacent to the linking N atom, (provided that the ring is not thereby quaternised) by (1-4C)alkyl;

RT is selected from a substituent from the group:

(RTa1) hydrogen, halogen, (1-4C)alkoxy, (2-4C)alkenyloxy, (2-4C)alkenyl, (2-4C)alkynyl, (3-6C)cycloalkyl, (3-6C)cycloalkenyl, (1-4C)alkylthio, amino, azido, cyano and nitro; or

(RTa2) (1-4C)alkylamino, di-(1-4C)alkylamino, and (2-4C)alkenylamino;

or RT is selected from the group

(RTb1) (1-4C)alkyl group which is optionally substituted by one substituent selected from hydroxy, (1-4C)alkoxy, (1-4C)alkylthio, cyano and azido; or

(RTb2) (1-4C)alkyl group which is optionally substituted by one substituent selected from (2-4C)alkenyloxy, (3-6C)cycloalkyl,and (3-6C)cycloalkenyl;

or RT is selected from the group

(RTc) a fully saturated 4-membered monocyclic ring containing 1 or 2 heteroatoms independently selected from O, N and S (optionally oxidised), and linked via a ring nitrogen or carbon atom;

and wherein at each occurrence of an RT substituent containing an alkyl, alkenyl, alkynyl, cycloalkyl or cycloalkenyl moiety in (RTa1) or (RTa2), (RTb1) or (RTb2), or (RTc) each such moiety is optionally substituted on an available carbon atom with one, two, three or more substituents independently selected from F, Cl, Br, OH and CN;

R_6 is cyano, $-COR_{12}$, $-COOR_{12}$, $-CONHR_{12}$, $-CON(R_{12})(R_{13})$, $-SO_2R_{12}$, $-SO_2NHR_{12}$, $-SO_2N(R_{12})(R_{13})$ or NO_2, wherein R_{12} and R_{13} are as defined hereinbelow;

R_7 is hydrogen, amino, (1-8C)alkyl, $-NHR_{12}$, $-N(R_{12})(R_{13})$, $-OR_{12}$ or $-SR_{12}$, (2-4C)alkenyl, -(1-8C)alkylaryl, mono-, di-, tri- and per-halo(1-8C)alkyl, $-(CH_2)p$(3-6C)cycloalkyl or $-(CH_2)p$(3-6C)cycloalkenyl wherein p is 0, 1 or 2;

R_8 is hydrogen, (3-6C)cycloalkyl, phenyl, benzyl, (1-5C)alkanoyl, (1-6C)alkyl (optionally substituted by substituents independently selected from (1-5C)alkoxycarbonyl, hydroxy, cyano, up to 3 halogen atoms and $-NR_{15}R_{16}$ (wherein R_{15} and R_{16} are independently selected from hydrogen, phenyl (optionally substituted with one or more substituents selected from halogen, (1-4C)alkyl and (1-4C)alkyl substituted with one, two, three or more halogen atoms) and (1-4C)alkyl (optionally substituted with one, two, three or more halogen atoms), or for any $N(R_{15})(R_{16})$ group, R_{15} and R_{16} may additionally be taken together with the nitrogen atom to which they are attached to form a pyrrolidinyl, piperidinyl or morpholinyl ring);

R_9 and R_{10} are independently selected from hydrogen and (1-4C)alkyl;

R_{11} is (1-4C)alkyl or phenyl;

R_{12} and R_{13} are independently selected from hydrogen, phenyl (optionally substituted with one or more substituents selected from halogen, (1-4C)alkyl and (1-4C)alkyl substituted with one, two, three or more halogen atoms) and (1-4C)alkyl (optionally substituted with one, two, three or more halogen atoms), or for any $N(R_{12})(R_{13})$ group, R_{12} and R_{13} may additionally be taken together with the nitrogen atom to which they are attached to form a pyrrolidinyl, piperidinyl or morpholinyl ring, which ring may be optionally substituted by a group selected

from (1-4C)alkyl, (1-4C)cycloalkyl, (1-4C)acyl, -COO(1-4C)alkyl, S(O)n(1-4C)alkyl (wherein n = 1 or 2), -COOAR1, -CS(1-4C)alkyl and –C(=S)O(1-4C)alkyl;

AR1 is an optionally substituted phenyl or optionally substituted naphthyl;

AR2 is an optionally substituted 5- or 6-membered, fully unsaturated monocyclic heteroaryl ring containing up to four heteroatoms independently selected from O, N and S (but not containing any O-O, O-S or S-S bonds), and linked via a ring carbon atom, or a ring nitrogen atom if the ring is not thereby quaternised;

AR2a is a partially hydrogenated version of AR2, linked via a ring carbon atom or linked via a ring nitrogen atom if the ring is not thereby quaternised;

AR2b is a fully hydrogenated version of AR2, linked via a ring carbon atom or linked via a ring nitrogen atom;

AR3 is an optionally substituted 8-, 9- or 10-membered, fully unsaturated bicyclic heteroaryl ring containing up to four heteroatoms independently selected from O, N and S (but not containing any O-O, O-S or S-S bonds), and linked via a ring carbon atom in either of the rings comprising the bicyclic system;

AR3a is a partially hydrogenated version of AR3, linked via a ring carbon atom, or linked via a ring nitrogen atom if the ring is not thereby quaternised, in either of the rings comprising the bicyclic system;

AR3b is a fully hydrogenated version of AR3, linked via a ring carbon atom, or linked via a ring nitrogen atom, in either of the rings comprising the bicyclic system;

AR4 is an optionally substituted 13- or 14-membered, fully unsaturated tricyclic heteroaryl ring containing up to four heteroatoms independently selected from O, N and S (but not containing any O-O, O-S or S-S bonds), and linked via a ring carbon atom in any of the rings comprising the tricyclic system;

AR4a is a partially hydrogenated version of AR4, linked via a ring carbon atom, or linked via a ring nitrogen atom if the ring is not thereby quaternised, in any of the rings comprising the tricyclic system;

CY1 is an optionally substituted cyclobutyl, cyclopentyl or cyclohexyl ring;

CY2 is an optionally substituted cyclopentenyl or cyclohexenyl ring;

wherein; optional substituents on AR1, AR2, AR2a, AR2b, AR3, AR3a, AR3b, AR4, AR4a, CY1 and CY2 are (on an available carbon atom) up to three substituents independently selected from (1-4C)alkyl {optionally substituted by substituents selected independently from hydroxy, trifluoromethyl, (1-4C)alkyl S(O)q- (q is 0, 1 or 2), (1-4C)alkoxy, .

(1-4C)alkoxycarbonyl, cyano, nitro, (1-4C)alkanoylamino, -CONRvRw or -NRvRw}, trifluoromethyl, hydroxy, halo, nitro, cyano, thiol, (1-4C)alkoxy, (1-4C)alkanoyloxy, dimethylaminomethyleneaminocarbonyl, di(N-(1-4C)alkyl)aminomethylimino, carboxy, (1-4C)alkoxycarbonyl, (1-4C)alkanoyl, (1-4C)alkylSO_2amino, (2-4C)alkenyl {optionally substituted by carboxy or (1-4C)alkoxycarbonyl}, (2-4C)alkynyl, (1-4C)alkanoylamino, oxo (=O), thioxo (=S), (1-4C)alkanoylamino {the (1-4C)alkanoyl group being optionally substituted by hydroxy}, (1-4C)alkyl S(O)q- (q is 0, 1 or 2) {the (1-4C)alkyl group being optionally substituted by one or more groups independently selected from cyano, hydroxy and (1-4C)alkoxy}, -CONRvRw or -NRvRw [wherein Rv is hydrogen or (1-4C)alkyl; Rw is hydrogen or (1-4C)alkyl];

and further optional substituents on AR1, AR2, AR2a, AR2b, AR3, AR3a, AR3b, AR4, AR4a, CY1 and CY2 (on an available carbon atom), and also on alkyl groups (unless indicated otherwise) are up to three substituents independently selected from trifluoromethoxy, benzoylamino, benzoyl, phenyl {optionally substituted by up to three substituents independently selected from halo, (1-4C)alkoxy or cyano}, furan, pyrrole, pyrazole, imidazole, triazole, pyrimidine, pyridazine, pyridine, isoxazole, oxazole, isothiazole, thiazole, thiophene, hydroxyimino(1-4C)alkyl, (1-4C)alkoxyimino(1-4C)alkyl, halo-(1-4C)alkyl, (1-4C)alkanesulfonamido, -SO_2NRvRw [wherein Rv is hydrogen or (1-4C)alkyl; Rw is hydrogen or (1-4C)alkyl]; and

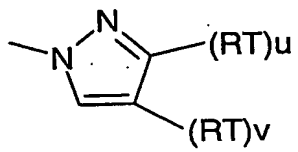
optional substituents on AR2, AR2a, AR2b, AR3, AR3a, AR3b, AR4 and AR4a are (on an available nitrogen atom, where such substitution does not result in quaternization) (1-4C)alkyl, (1-4C)alkanoyl {wherein the (1-4C)alkyl and (1-4C)alkanoyl groups are optionally substituted by (preferably one) substituents independently selected from cyano, hydroxy, nitro, trifluoromethyl, (1-4C)alkyl S(O)q- (q is 0, 1 or 2), (1-4C)alkoxy, (1-4C)alkoxycarbonyl, (1-4C)alkanoylamino, -CONRvRw or -NRvRw [wherein Rv is hydrogen or (1-4C)alkyl; Rw is hydrogen or (1-4C)alkyl]}, (2-4C)alkenyl, (2-4C)alkynyl, (1-4C)alkoxycarbonyl or oxo (to form an N-oxide).

2. A compound of the formula (I) or a pharmaceutically-acceptable salt, or in-vivo hydrolysable ester thereof, as claimed in claim 1, wherein group C is selected from groups D, E, H and I.

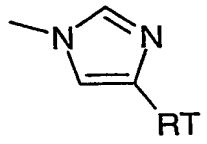
3. A compound of the formula (I) or a pharmaceutically-acceptable salt, or in-vivo

hydrolysable ester thereof, as claimed in claim 1 or claim 2, wherein R_1a and R_1b are independently selected from -NHCO(1-4C)alkyl, -NHCO(1-4C)cycloalkyl , -NHCS(1-4C)alkyl, -N(R_5)-HET-1 and HET-2.

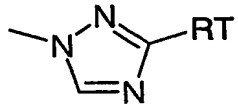
4. A compound of the formula (I) or a pharmaceutically-acceptable salt, or in-vivo hydrolysable ester thereof, as claimed in claim 1, claim 2 or claim 3, wherein HET-2A is selected from the structures (Za) to (Zf) below:



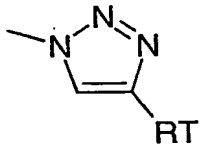
(Za)



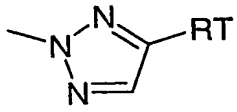
(Zb)



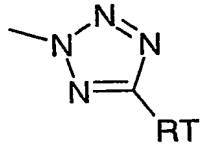
(Zc)



(Zd)



(Ze)



(Zf)

wherein u and v are independently 0 or 1.

5. A compound of the formula (I) or a pharmaceutically-acceptable salt, or in-vivo hydrolysable ester thereof, as claimed in claim 4 wherein RT is selected from

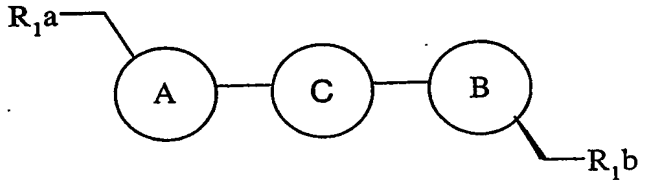
(a) hydrogen;
(b) halogen;
(c) cyano;
(d) (1-4C)alkyl;
(e) monosubstituted (1-4C)alkyl;
(f) disubstituted (1-4C)alkyl, and
trisubstituted (1-4C)alkyl.

6. A compound of the formula (I) or a pharmaceutically-acceptable salt, or in-vivo hydrolysable ester thereof, as claimed in any preceding claim wherein at least one of A and B

is an oxazolidinone.

7. A compound of the formula (I) or a pharmaceutically-acceptable salt, or in-vivo hydrolysable ester thereof, as claimed in any preceding claim wherein both A and B are oxazolidinones.

8. A compound of the formula (IA) or a pharmaceutically-acceptable salt, or in-vivo hydrolysable ester thereof, as claimed in any preceding claim.



(IA)

9. A pro-drug of a compound as claimed in any one of the previous claims.

10. A method for producing an antibacterial effect in a warm blooded animal which comprises administering to said animal an effective amount of a compound of the invention as claimed in any one of claims 1 to 9, or a pharmaceutically-acceptable salt, or in-vivo hydrolysable ester thereof.

11. A compound of the invention as claimed in any one of claims 1 to 9, or a pharmaceutically-acceptable salt, or in-vivo hydrolysable ester thereof, for use as a medicament.

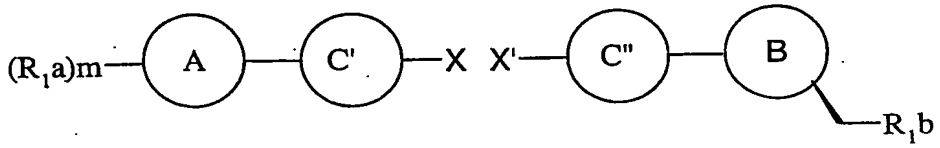
12. The use of a compound of the invention as claimed in any one of claims 1 to 9, or a pharmaceutically-acceptable salt, or in-vivo hydrolysable ester thereof, in the manufacture of a medicament for use in the production of an antibacterial effect in a warm blooded animal.

13. A pharmaceutical composition which comprises a compound of the invention as claimed in any one of claims 1 to 14, or a pharmaceutically-acceptable salt or an in-vivo hydrolysable ester thereof, and a pharmaceutically-acceptable diluent or carrier.

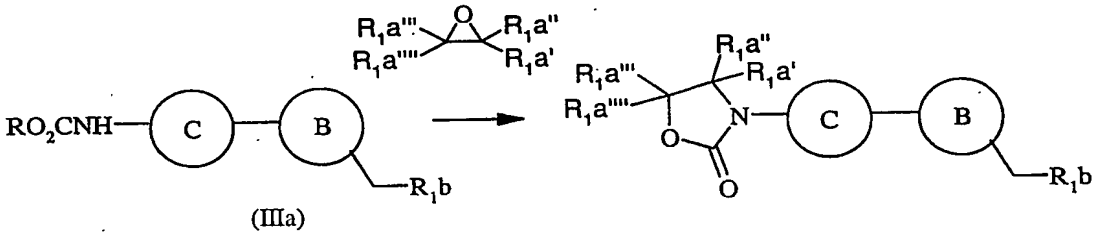
14. A process for the preparation of a compound of formula (I) as claimed in claim 1 or pharmaceutically acceptable salts or in-vivo hydrolysable esters thereof, which process comprises one of processes (a) to (d):

(a) by modifying a substituent in, or introducing a substituent into another compound of the invention by using standard chemistry;

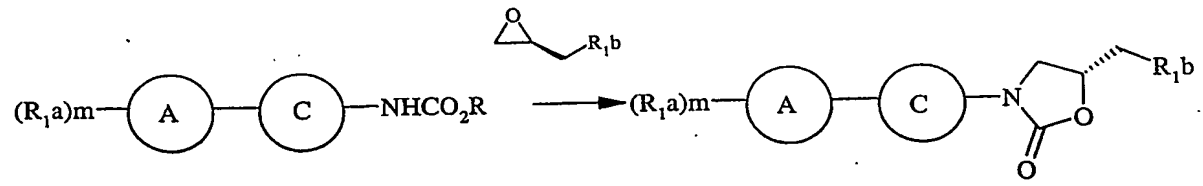
b) by reaction of a molecule of a compound of formula (IIa) with a molecules of a compound of formula (IIb) wherein X and X' are leaving groups useful in palladium coupling and are chosen such that an aryl-aryl, heteroaryl-aryl, or heteroaryl-heteroaryl bond replaces the aryl-X (or heteroaryl-X) and aryl-X' (or heteroaryl-X') bonds.



c) by reaction of a (hetero)biaryl derivative (IIIa) or (IIIb) carbamate with an appropriately substituted oxirane (wherein 0, 1, or 2 of R_1a'-R_1a'''' are substitutents as defined for R_1a and the remainder are hydrogen) to form an oxazolidinone ring at the undeveloped aryl position;



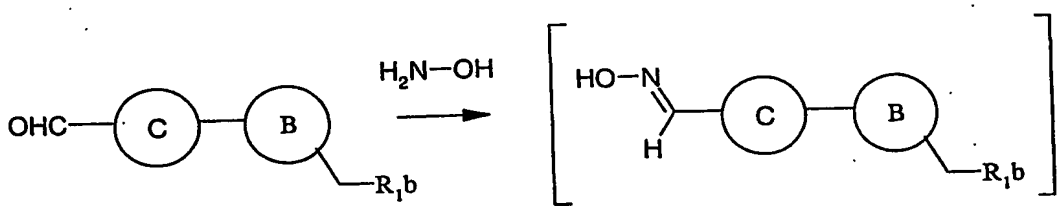
(IIIa)



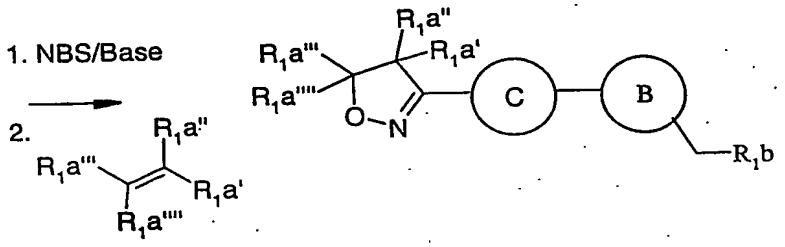
(IIIb)

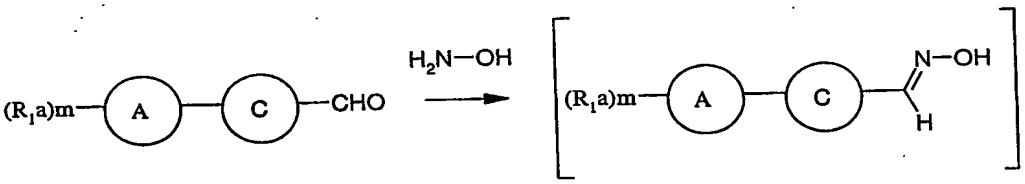
or by variations on this process in which the carbamate is replaced by an isocyanate or by an amine or/and in which the oxirane is replaced by an equivalent reagent X-$C(R_1a')(R_1a'')C(R_1a''')$(O-optionally protected)$(R_1a'''')$ or X-CH_2CH(O-optionally protected)CH_2R_1b where X is a displaceable group.

e) by reaction of a (hetero)biaryl derivative (IVa) or (IVb) to form an isoxazoline ring at the undeveloped aryl position;

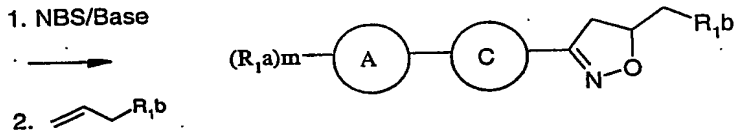


(IVa) (IVa')

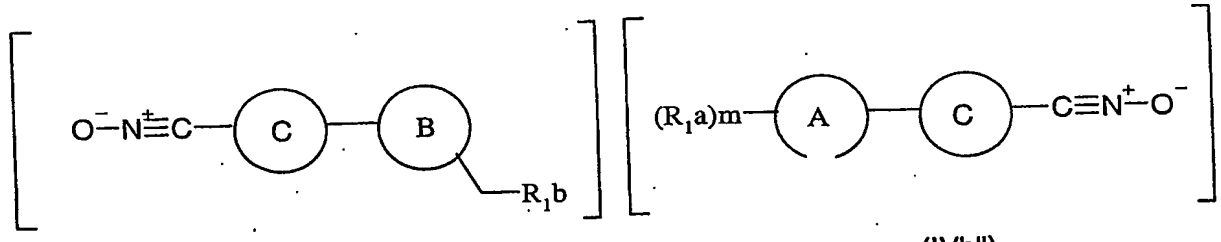




(IVb) (IVb')



or by variations on this process in which the reactive intermediate (a nitrile oxide IVa'' or IVb'') is obtained other than by oxidation of an oxime (IVa') or (IVb').

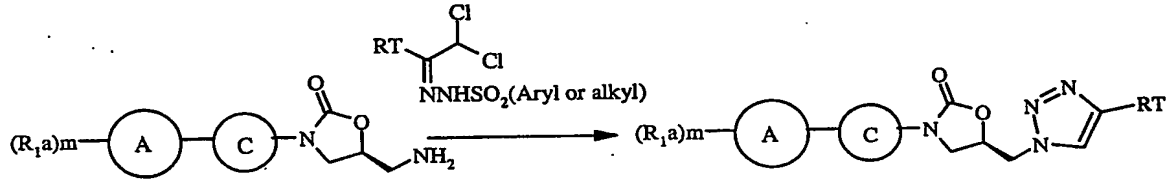


(IVa") (IVb")

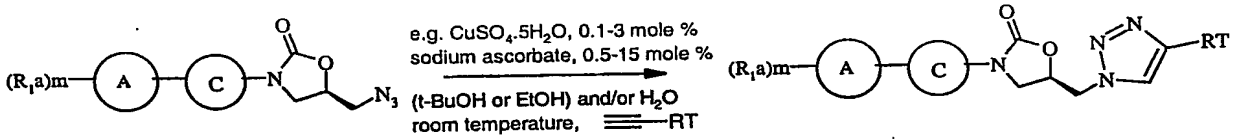
(e) for HET as optionally substituted 1,2,3-triazoles, compounds of the formula (I) may be made by cycloaddition via the azide (wherein e.g. Y in (II) is azide) to acetylenes, or to

acetylene equivalents such as optionally substituted cylcohexa-1,4-dienes or optionally substituted ethylenes bearing eliminatable substituents such as arylsulfonyl;

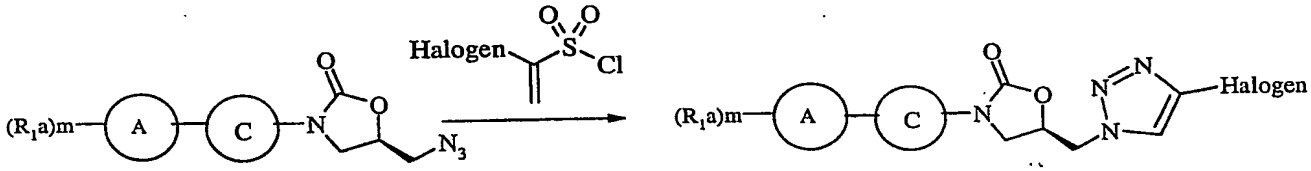
(f) for HET as 4-substituted 1,2,3-triazole compounds of formula (I) may be made by reacting aminomethyloxazolidinones with 1,1-dihaloketone sulfonylhydrazones for instance



(g) for HET as 4-substituted 1,2,3-triazole compounds of formula (I) may also be made by reacting azidomethyl oxazolidinones with terminal alkynes using Cu(I) catalysis in e.g. aqueous alcoholic solution at ambient temperatures to give 4-substituted 1,2,3-triazoles



(h) for HET as 4-halogenated 1,2,3-triazole compounds of formula (I) may also be made by reacting azidomethyl oxazolidinones with halovinylsulfonyl chlorides at a temperature between 0 °C and 100 °C either neat or in an inert diluent such as chlorobenzene, chloroform or dioxan; for instance



PCT Application

GB0305087